# QUALI NAO? SONO TUTTI UGUALI?


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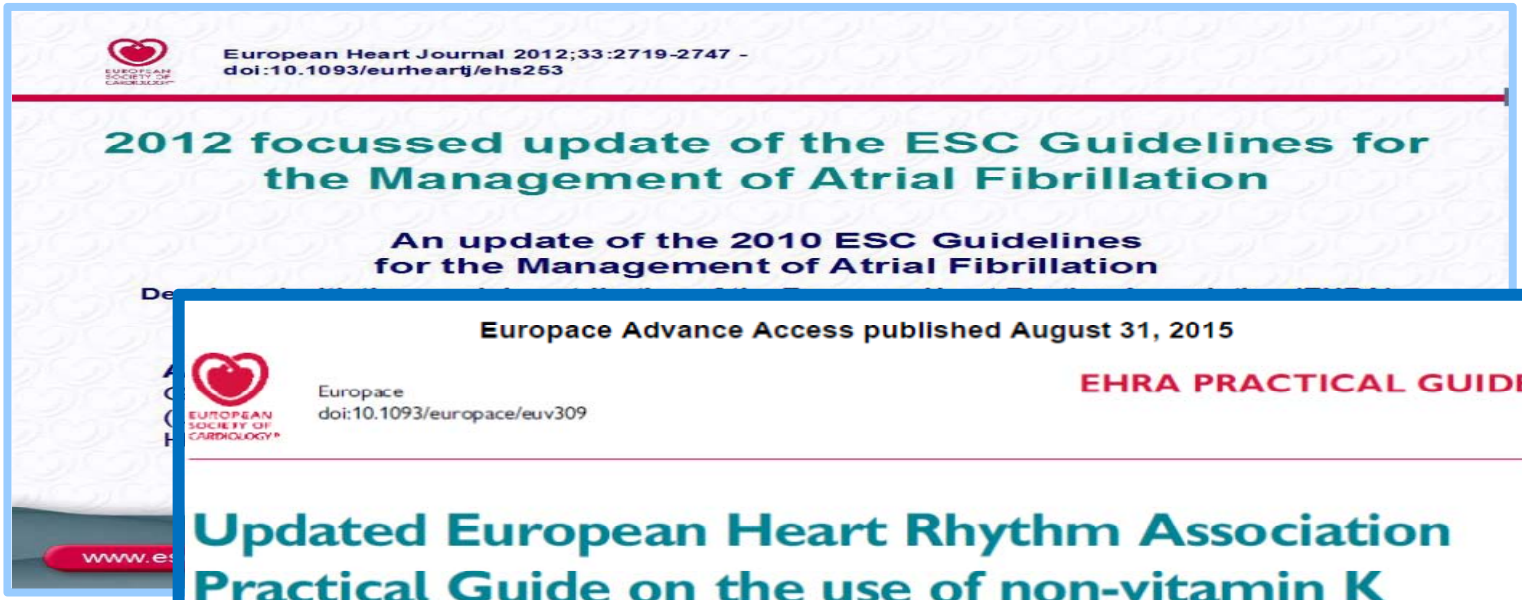

European Heart Journal 2012;33:2719-2747 -
doi:10.1093/eurheartj/ehs253

## 2012 focussed update of the ESC Guidelines for the Management of Atrial Fibrillation

### An update of the 2010 ESC Guidelines for the Management of Atrial Fibrillation

Europace Advance Access published August 31, 2015

Europace
doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

# Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Hein Heidbuchel[1]*, Peter Verhamme[2], Marco Alings[3], Matthias Antz[4], Hans-Christoph Diener[5], Werner Hacke[6], Jonas Oldgren[7], Peter Sinnaeve[2], A. John Camm[8], and Paulus Kirchhof[9,10]

Advisors:, Azhar Ahmad, M.D. (Boehringer Ingelheim Pharma), Jutta Heinrich-Nols, M.D. (Boehringer Ingelheim Pharma), Susanne Hess, M.D. (Bayer Healthcare Pharmaceuticals), Markus Müller, M.D., Ph.D. (Pfizer Pharma), Felix Münzel, Ph.D. (Daiichi-Sankyo Europe), Markus Schwertfeger, M.D. (Daiichi-Sankyo Europe), Martin Van Eickels, M.D. (Bayer Healthcare Pharmaceuticals), and Isabelle Richard-Lordereau, M.D. (Bristol Myers Squibb/Pfizer)

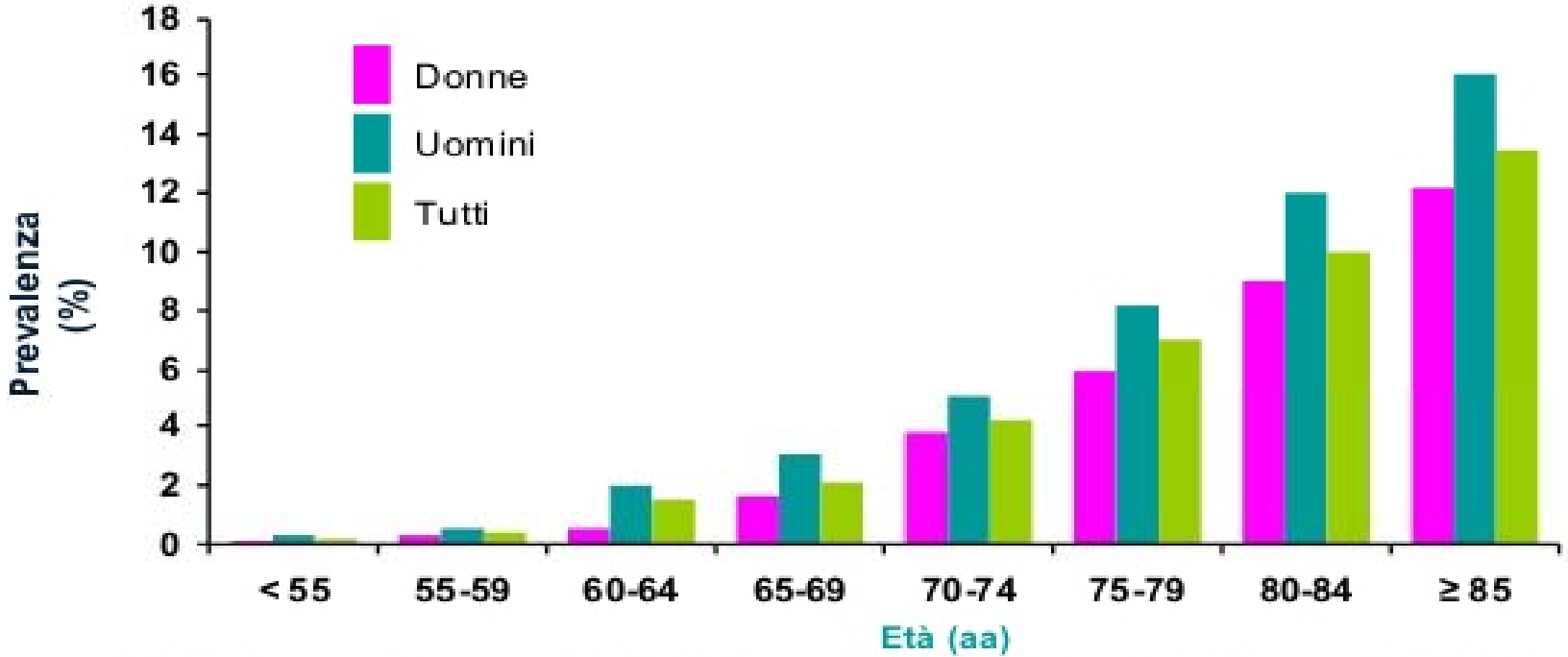
2014 AHA/

A Report of the

Forc

*Developed in Collaboration With the Society of Thoracic Surgeons*

# La prevalenza della Fibrillazione Atriale cresce in rapporto all'età




*MarketScan Commercial Claims and Encounters database and Medicare Supplemental database (USA)*

Naccarelli GV et al. *Am J Cardiol*. 2009;104(11):1534-9

# The Consequences of AF

## Mortality

- 2× increased risk independent of comorbid CV disease
- Sudden death in HF and HCM

## Thromboembolism

- Stroke: 4.5× increased risk
- Microemboli: reduced cognitive function
- Prothrombotic state

## Hospitalizations

- Most common arrhythmia requiring hospitalization
- 2-3× increased risk for hospitalization

## Reduced QoL

- Palpitations, dyspnea, fatigue, reduced exercise tolerance

## Impaired Hemodynamics

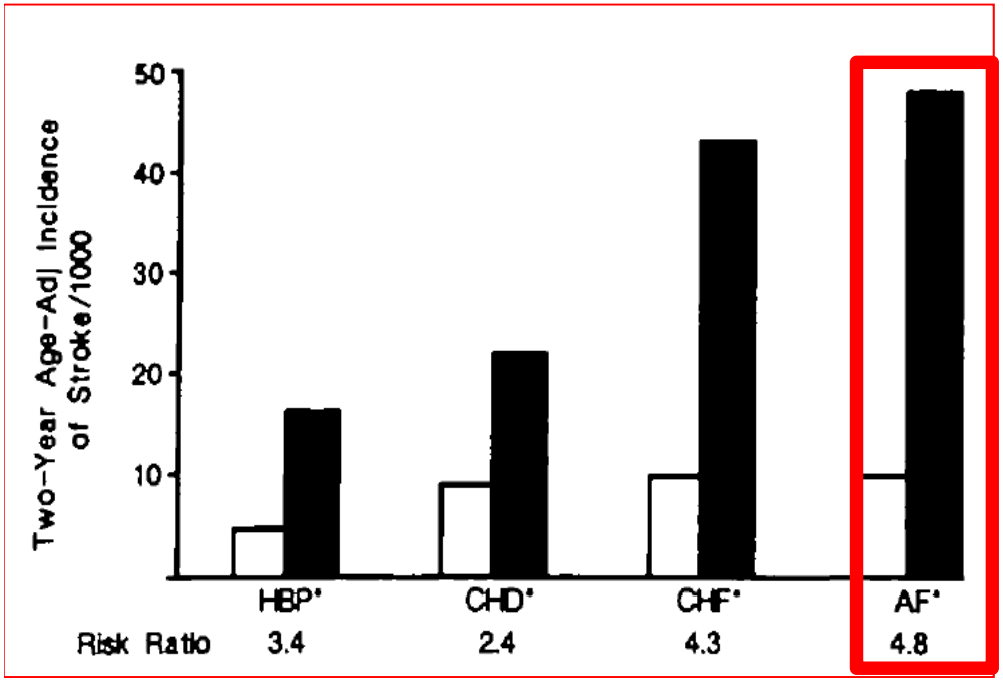
- Loss of atrial kick
- Irregular ventricular contractions
- HF
- Tachycardia-induced cardiomyopathy

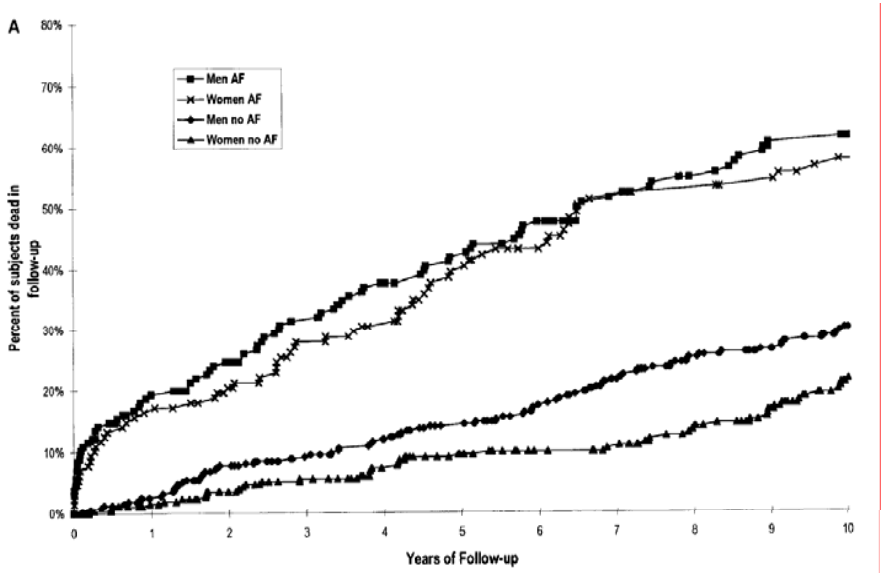
HCM=hypertrophic cardiomyopathy.

Van Gelder et al. *Europace*. 2006;8:943-949; Narayan et al. *Lancet*. 1997;350:943-950; Wattigney et al. *Circulation*. 2003;108:711-716; Wyse et al. *Circulation*. 2004;109:3089-3095; Favale et al. *PACE*. 2003;26:637-639.

# Fibrillazione Atriale (FA) e rischio di ictus ischemico

## Lo studio Framingham




**Ictus**
**RR 4,8**

**Mortalità**
**OR 1,5 men**
**OR 1,9 women**

*Stroke*. 1991;22:983-988

# La Fibrillazione Atriale aumenta il rischio di Ictus Cerebri

- La FA predispone a fenomeni di embolia cerebrale e si associa ad una condizione pro-trombotica. Nel complesso I pazienti con FA hanno un rischio di Ictus 5 volte superiore alla popolazione generale.
- Gli Ictus determinati dalla FA sono caratterizzati da una maggiore gravità clinica, da un maggiore grado di disabilità residua e si accompagnano ad una mortalità a 30 giorni del 25% e ad una mortalità ad un anno del 50%.
- Il rischio di ictus è aumentato in tutte le forma di FA


1.Watson T, et al. *Lancet* 2009;373:155-166.
2. Wolf PA, et al. *Stroke* 1991;22:983-988.
3. Atlas of Heart Disease and Stroke, World Health Organization, September 2004.
4. Lin HJ, et al. *Stroke* 1996;27:1760-1764. 5. Marini C, et al. *Stroke* 2005;36:1115-1119.
6. Rosamond W, et al. *Circulation* 2008;117:e25-146.
7. Hart RG, et al. *J Am Coll Cardiol* 2000;35:183-187.

# Impatto economico

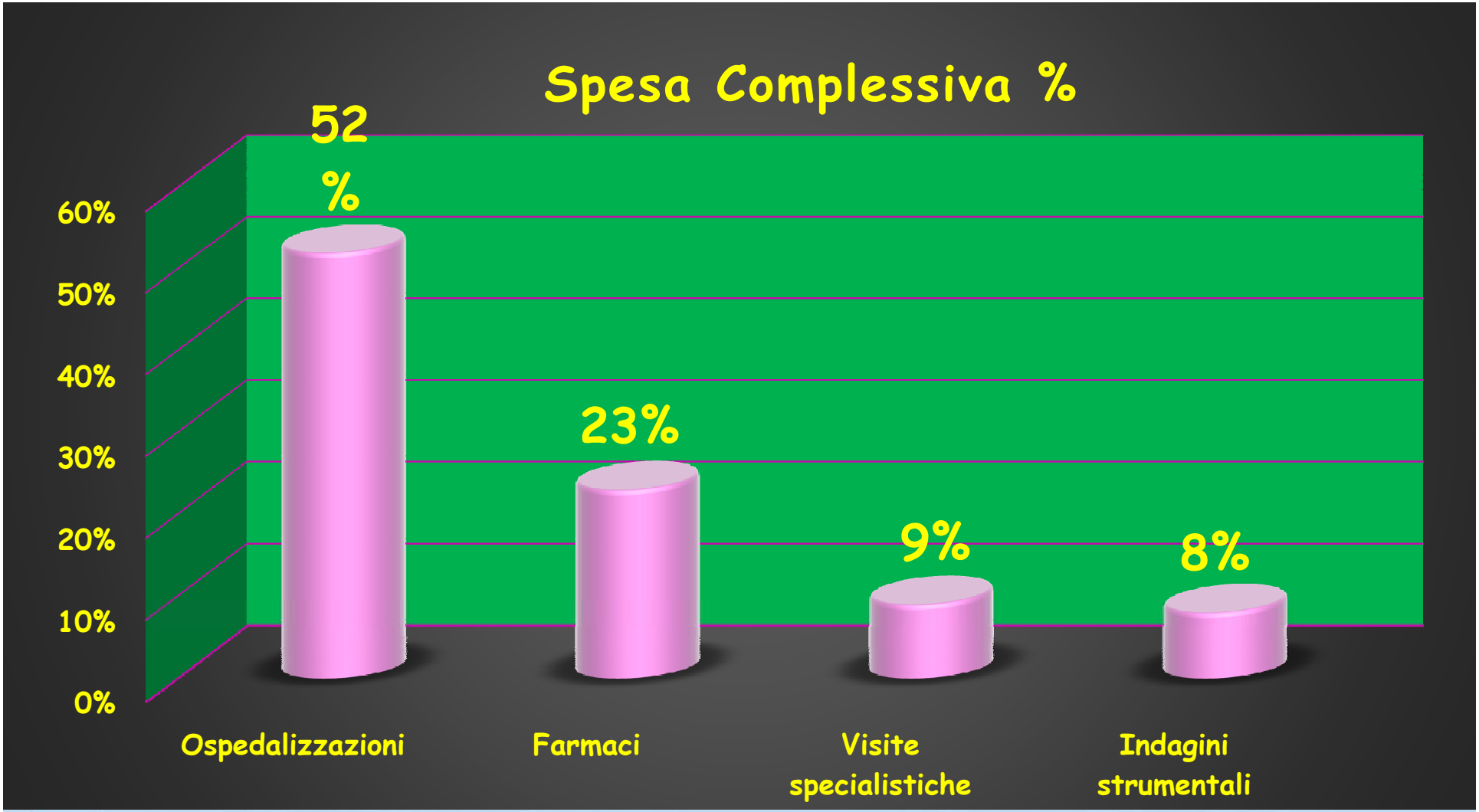
- La FA ha un impatto notevole nell'utilizzo delle risorse economiche dal momento che è condizione diffusa e in continua crescita nella popolazione generale e inoltre per la sua morbilità è una causa frequente di accesso alle strutture ospedaliere e di ricovero

- Il costo complessivo è fortemente influenzato da

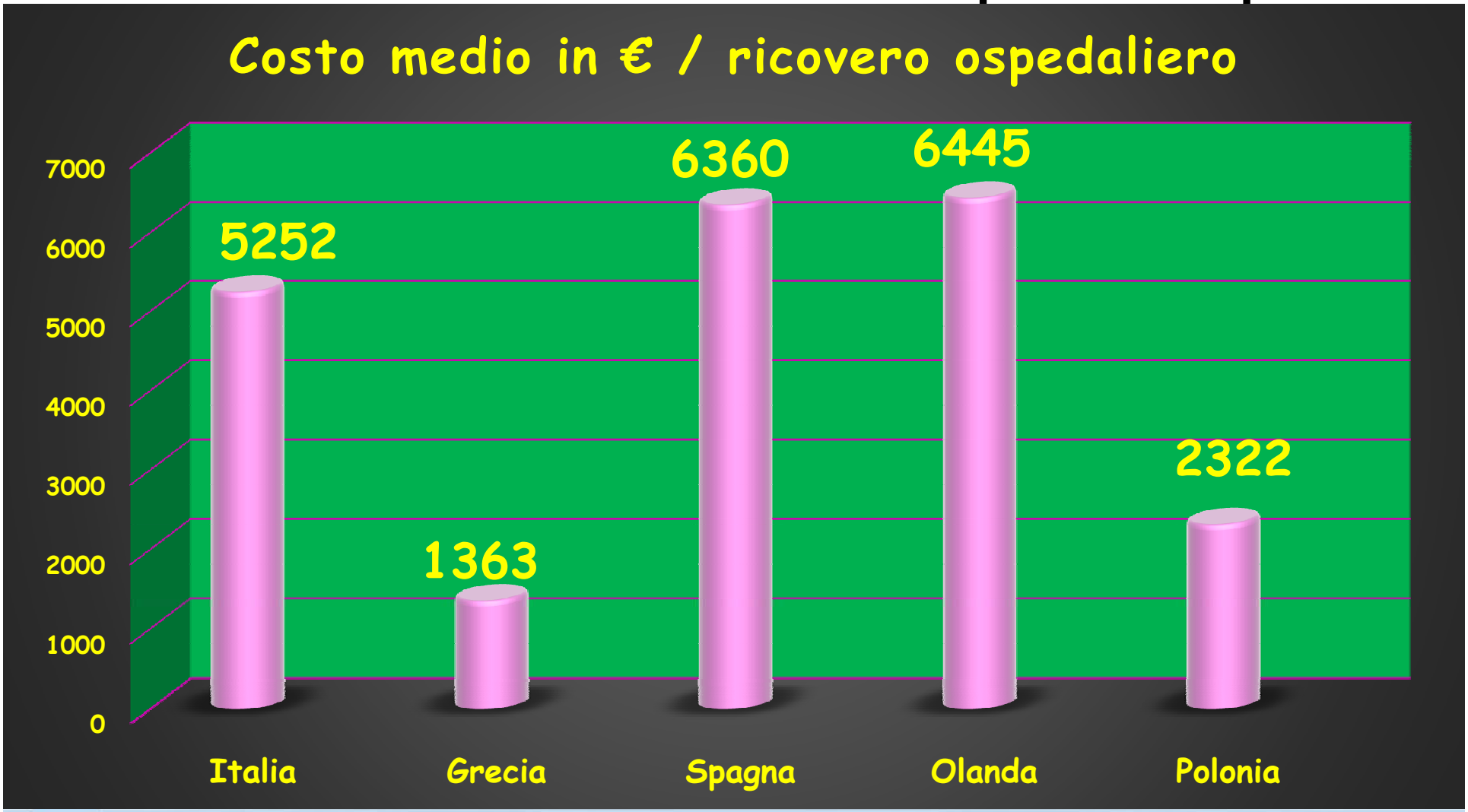
  1) cure iniziali al momento della diagnosi

  2) gestione cronica dei pazienti (impiego e monitoraggio TAO; profilassi farmacologica delle recidive)

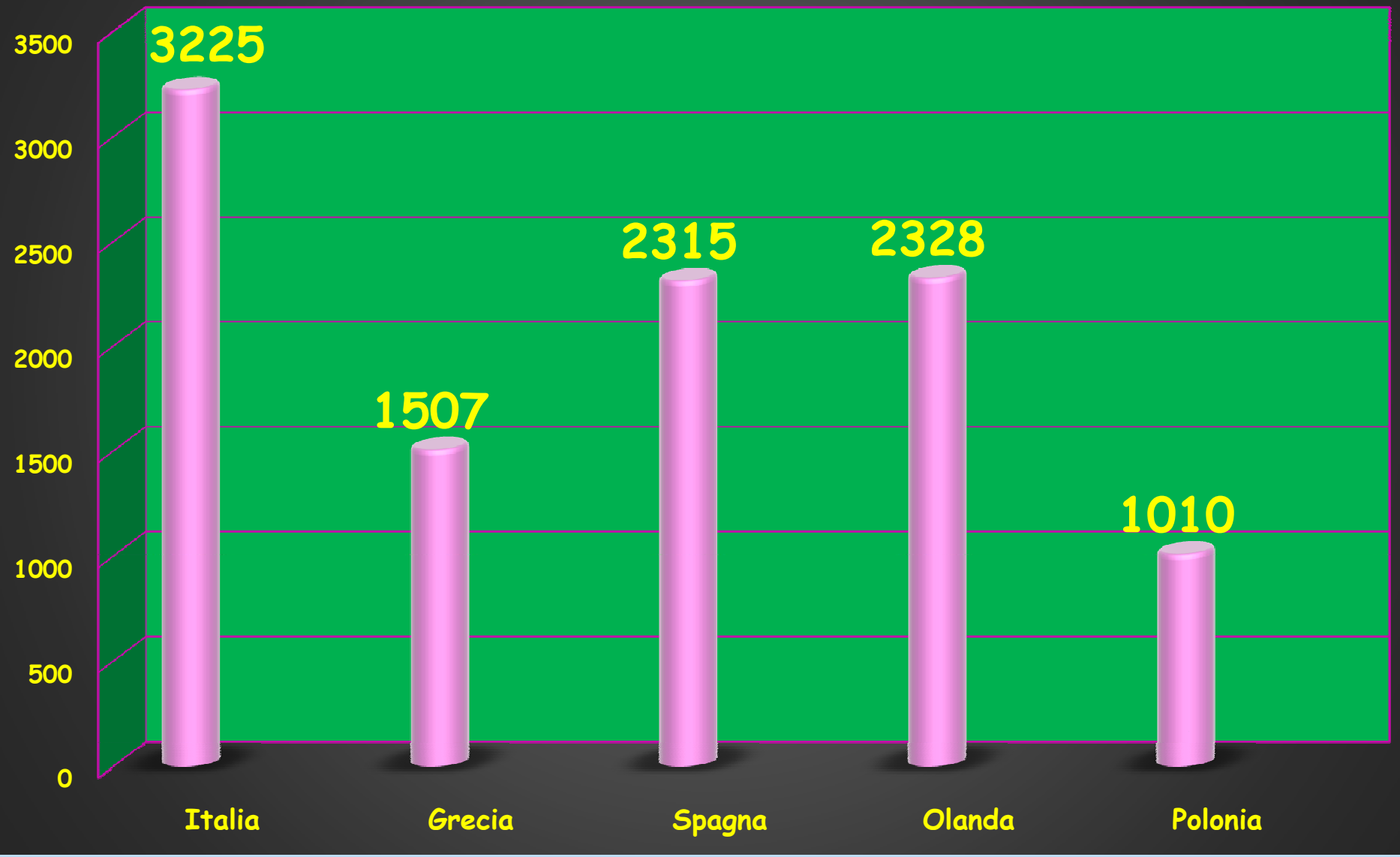
- **Studio COCAF** → ha stimato costo annuale di ogni singolo paziente pari a 3000 €



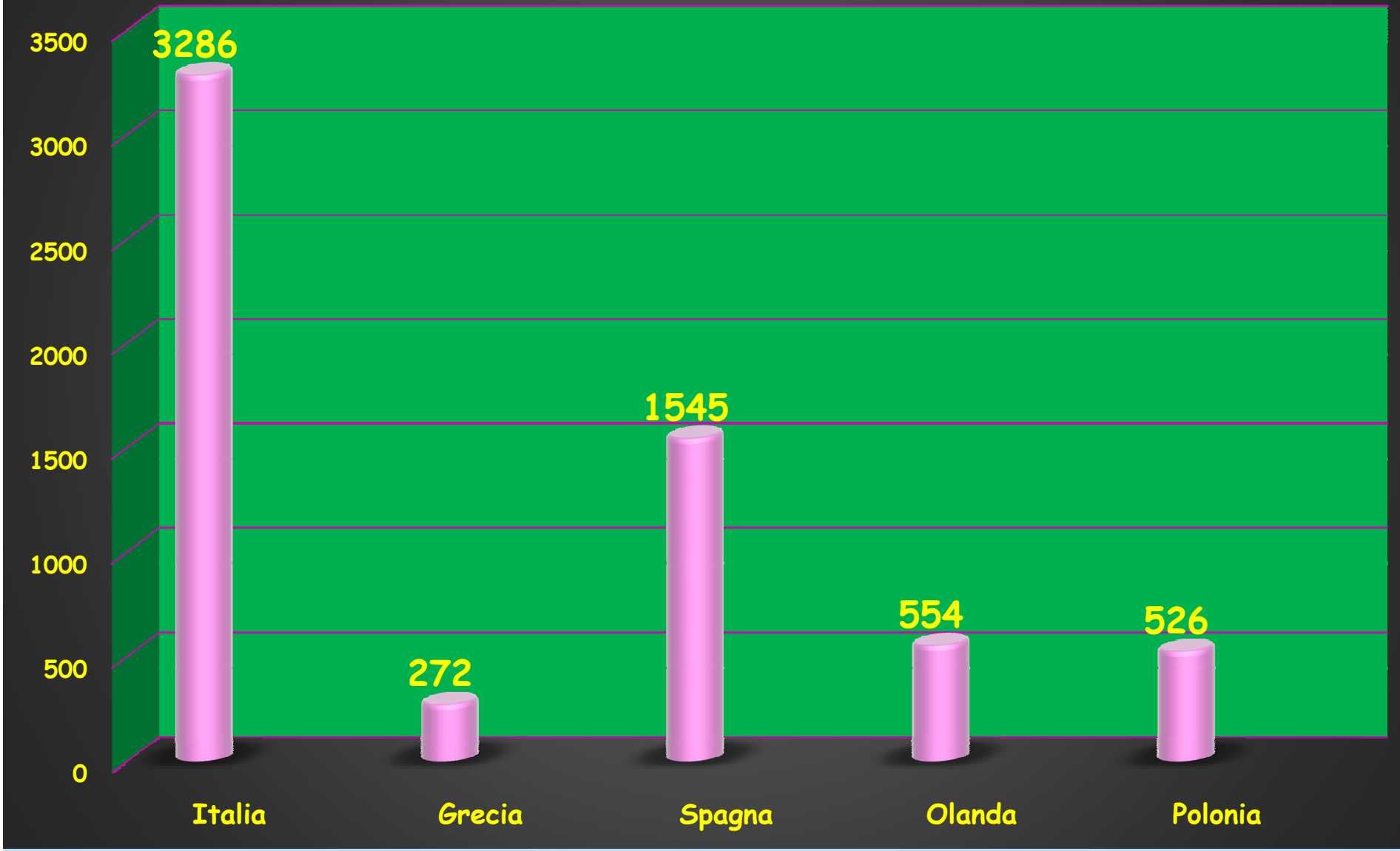
- Studio Euro Heart Survey → ha stimato l'impatto economico in 5 paesi Europei



# Costo medio annuo in €/paziente



# Costo complessivo annuo (milioni di €)



# Opportunistic Screening

| Recommendations for screening AF | | |
|---|---|---|
| **Recommendations** | **Class[a]** | **Level[b]** |
| Opportunistic screening for AF in patients ≥65 years of age using pulse-taking followed by an ECG is recommended to allow timely detection of AF. | I | B |

[a]Class of recommendation. [b]Level of evidence.
AF = atrial fibrillation; LoE = level of evidence.

www.escardio.org/guidelines

European Heart Journal 2012;33:2719-2747 - doi:10.1093/eurheartj/ehs253

EUROPEAN SOCIETY OF CARDIOLOGY®

# Valutazione iniziale del paziente con FA

## Rischio Trombo-embolico

$CHA_2DS_2Vasc$ Score
(I - B)

## Rischio di emorragia

HAS-BLED, HEMORR2HAGES, RIETE, ATRIA Score, ORBIT
(bassa performance e predittività)

2014 AHA/ACC/HRS Atrial Fibrillation Guideline

# Many Stroke Risk Factors Are Also Risk Factors for Bleeding

| | Risk Factor for Stroke* | Risk Factor for Anticoagulant-Related Bleeding* |
|---|---|---|
| Advanced age[a-d] | ✓ | ✓ |
| History of hypertension[a,c,d] | ✓ | ✓ |
| History of MI or ischemic heart disease[a,c] | ✓ | ✓ |
| Cerebrovascular disease[a-d] | ✓ | ✓ |
| Anemia[c,d] | | ✓ |
| Previous history of bleeding[c,d] | | ✓ |
| Kidney or liver dysfunction[d] | | ✓ |
| Concomitant use of antiplatelets[c,d] | | ✓ |

*Not exhaustive

**Higher stroke risk = higher bleeding risk**


a. Lip GY, et al. *Chest.* 2010;137(2):263-272.
b. Hylek EM, et al. *Ann Intern Med.* 1994;120(11):897-902.
c. Hughes M, et al. *QJM.* 2007;100(10):599-607.
d. Pisters R, et al. *Chest.* 2010;138(5):1093-1100.

## Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

| | Eligible | Contra-indicated |
|---|---|---|
| Mechanical prosthetic valve | | ✓ |
| Moderate to severe mitral stenosis (usually of rheumatic origin) | | ✓ |
| Mild to moderate other native valvular disease | ✓ | |
| Severe aortic stenosis | ✓ Limited data. Most will undergo intervention | |
| Bioprosthetic valve[a] | ✓ (except for the first 3 months post-operatively) | |
| Mitral valve repair[a] | ✓ (except for the first 3–6 months post-operatively) | |
| PTAV and TAVI | ✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk) | |
| Hypertrophic cardiomyopathy | ✓ (but no prospective data) | |

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Europace Advance Access published August 31, 2015
Europace doi:10.1093/europace/euv309
EHRA PRACTICAL GUIDE

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European Heart Journal Advance Access published September 28, 2014

European Heart Journal
doi:10.1093/eurheartj/ehu352

CURRENT OPINION

# What is 'valvular' atrial fibrillation? A reappraisal

**Raffaele De Caterina[1] and A. John Camm[2]***

[1]Institute of Cardiology and Center of Excellence on Aging, G. D'Annunzio University – Chieti, and G. Monasterio Foundation, Pisa, Italy; and [2]Division of Clinical Sciences, St George's University of London, London, UK

*Received 22 April 2014; revised 18 July 2014; accepted 6 August 2014*

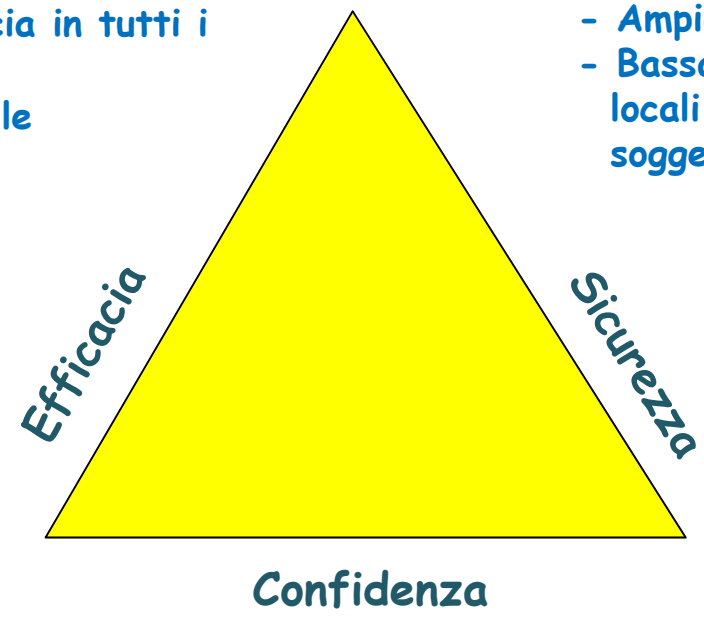
*We propose the term 'mechanical and rheumatic mitral valvular AF' (acronym: MARM-AF) as an accurate description of a disease entity worthy of being kept separated from other forms of AF, but with possible internal differences between the two conditions here encompassed.*

# TERAPIA ANTICOAGULANTE

- Lo scenario
- I NAO: nuove prospettive
- I NAO: caratteristiche a confronto
- I NAO: profilo di sicurezza

# Caratteristiche ideali di un agente antitrombotico nella FA

- Dimostrata efficacia in tutti i sottogruppi di FA
- Risposta prevedibile

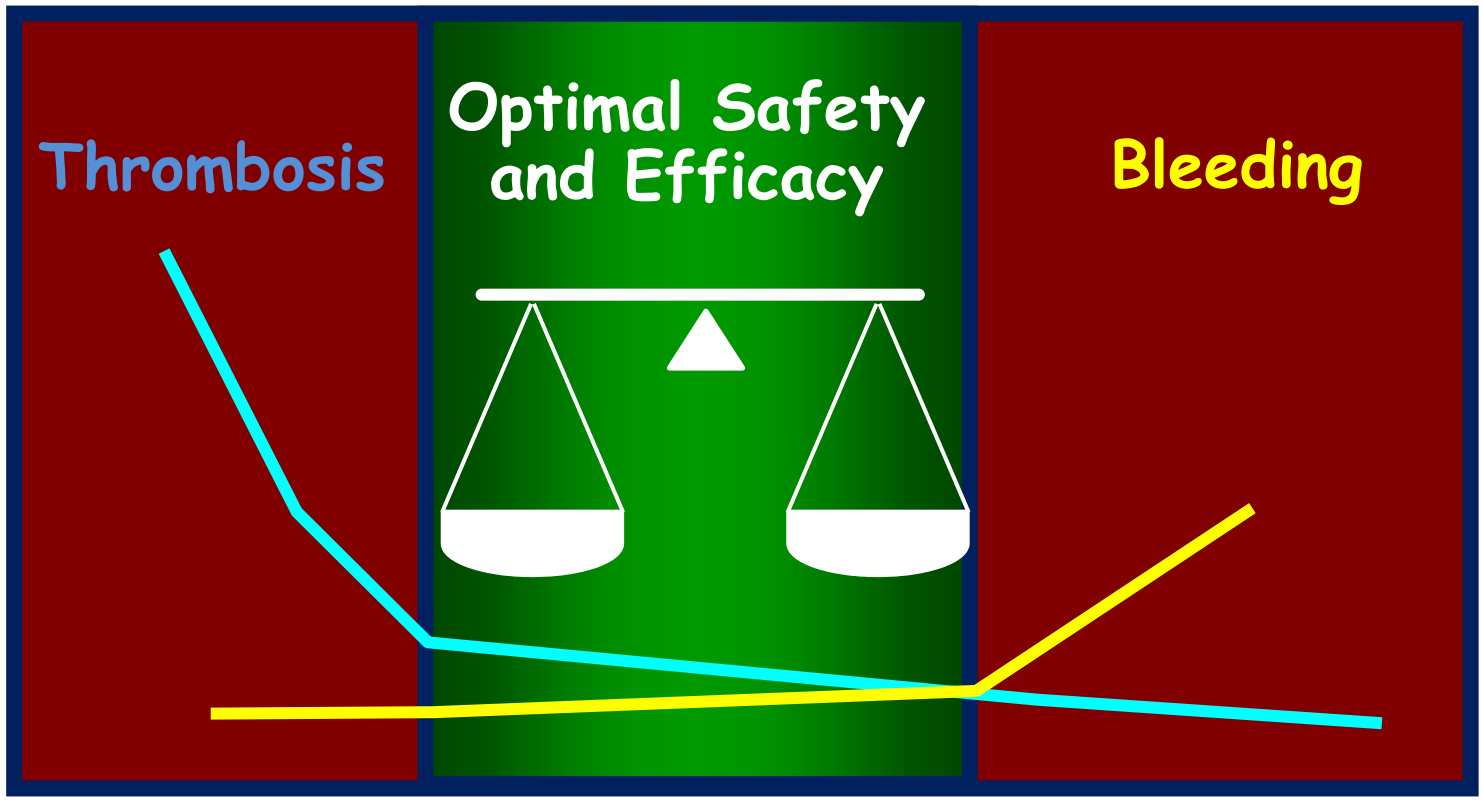



- Ampia finestra terapeutica
- Bassa incidenza e severità di effetti locali e sistemici (anche nei tipici soggetti con FA: anziani)

*Dose orale fissa*
- Assenza di interazione con farmaci e alimenti
- Monitoraggio coaugulativo non richiesto
- Ben tollerata dai pazienti

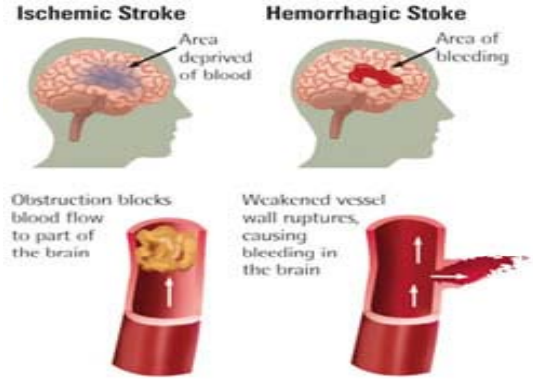
Gregory et al The SPORTIF Programmme Path Haemost Thromb 2005

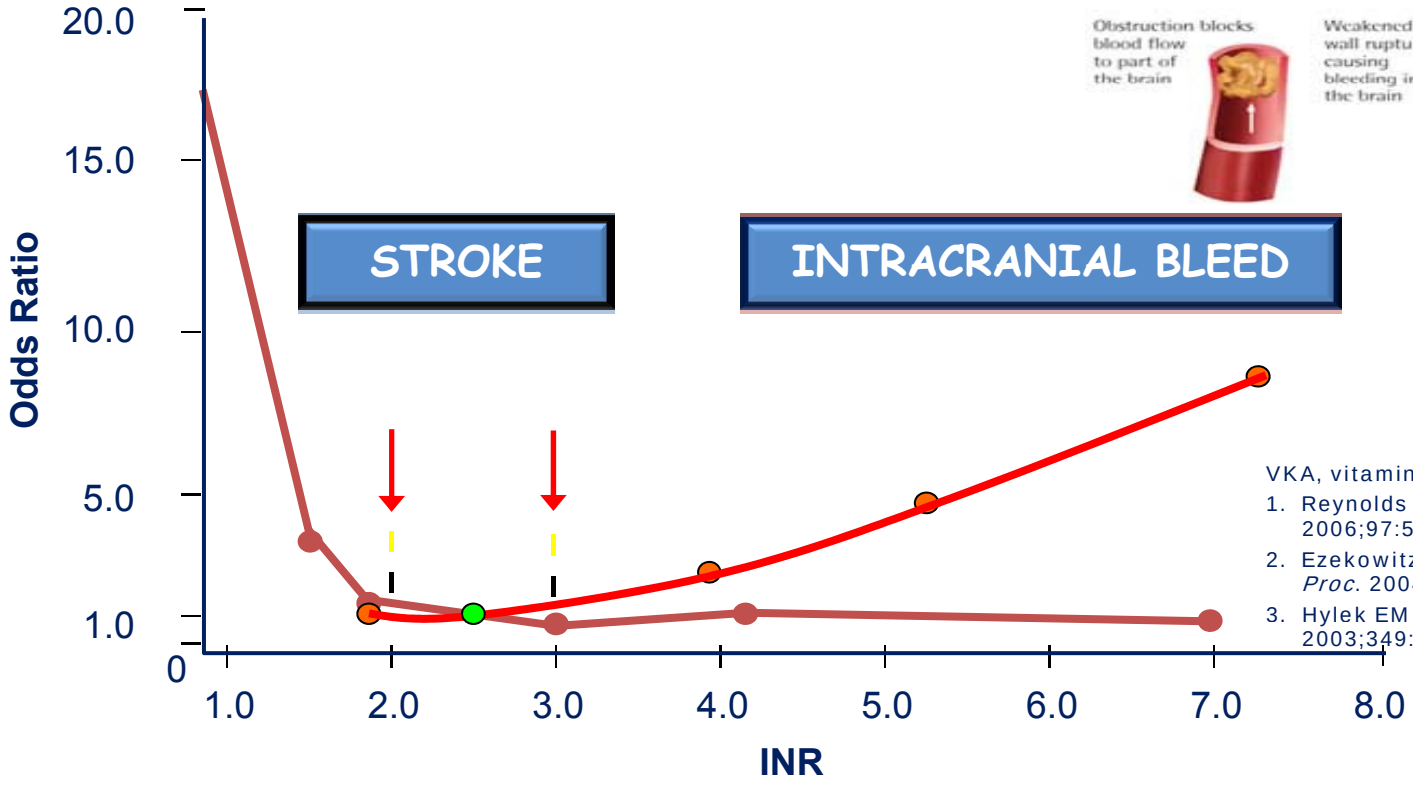
# The Search for an Anticoagulant That Balances Safety and Efficacy



# BARRIERS ASSOCIATED WITH VKA USE

- The most common barrier to VKA use is a concern over the risk of bleeding[1]
- VKAs have a narrow therapeutic range[2,3]




VKA, vitamin K antagonist.


1. Reynolds MR et al. *Am J Cardiol.* 2006;97:538-43.
2. Ezekowitz MD et al. *Mayo Clin Proc.* 2004;79:904-913.
3. Hylek EM et al. *N Engl J Med.* 2003;349:1019-1026.

# Limiti della terapia con VKA

Risposta Imprevedibile

Ristretta finestra terapeutica (INR range 2-3)

Farmaco resistenza

Monitoraggio periodico della coagulazione

La terapia con VKA presenta numerose limitazioni che ne rendono difficile l'utilizzo

Numerose interazioni farmacologiche

Numerose interazioni con il cibo

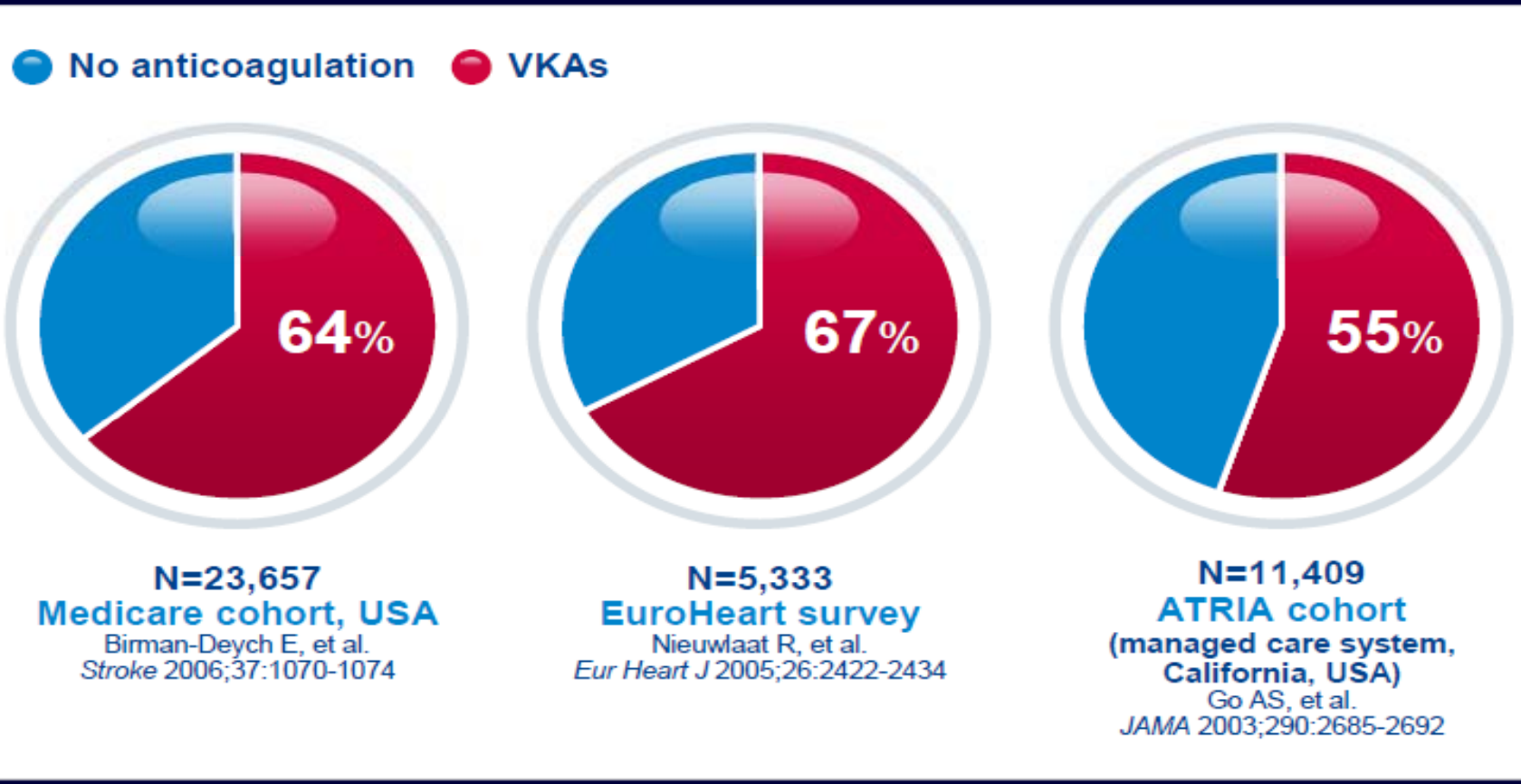
Azione a lenta insorgenza/cessazione

Frequenti aggiustamenti di dose

Solo 50% di pazienti elegibili ricevono il warfarin

1. Ansell J, et al. *Chest* 2008;133;160S-198S; 2. Umer Ushman MH, et al. *J Interv Card Electrophysiol* 2008; 22:129-137; Nutescu EA, et al. *Cardiol Clin* 2008; 26:169-187.

# Management of AF in clinical practice: Prescription of VKAs




**N=23,657**
**Medicare cohort, USA**
Birman-Deych E, et al.
*Stroke* 2006;37:1070-1074

**N=5,333**
**EuroHeart survey**
Nieuwlaat R, et al.
*Eur Heart J* 2005;26:2422-2434

**N=11,409**
**ATRIA cohort**
**(managed care system, California, USA)**
Go AS, et al.
*JAMA* 2003;290:2685-2692

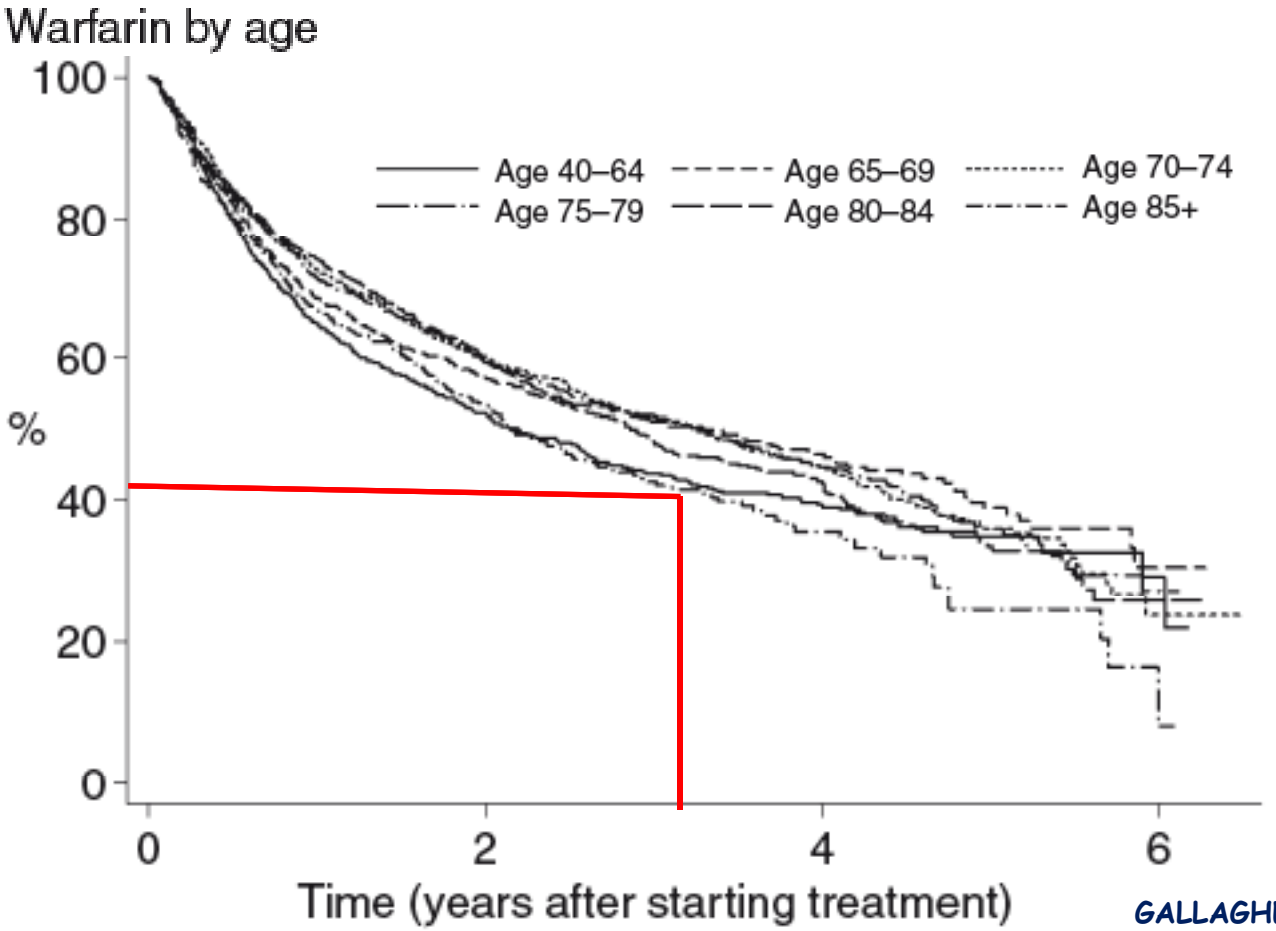
# Time in Therapeutic Range (TTR) INR Data

## Warfarin

| INR range | Median (25th, 75th) |
|---|---|
| <1.5 | 2.7 (0.0 – 9.0) |
| 1.5 to <1.8 | 7.9 (3.5 – 14.0) |
| 1.8 to <2.0 | 9.1 (5.3 – 13.6) |
| **2.0 to 3.0** | **57.8 (43.0 – 70.5)** |
| >3.0 to 3.2 | 4.0 (1.9 – 6.5) |
| >3.2 to 5.0 | 7.9 (3.3 – 13.8) |
| >5.0 | 0.0 (0.0 – 0.5) |

Based on Rosendaal method with all INR values included
Based on Safety Population

# Rinuncia alla terapia anticoagulante nei pazienti con FA




GALLAGHER A:M: JTH 2008

# Time in Therapeutic Range (TTR)

## Qualità della TAO:

Per **TTR** si intende il **T**ime in **T**herapeuc INR **R**ange (%)

**Esprime la qualità della TAO,** indicando **quanto tempo il paziente passa all'interno del suo range terapeutico.**

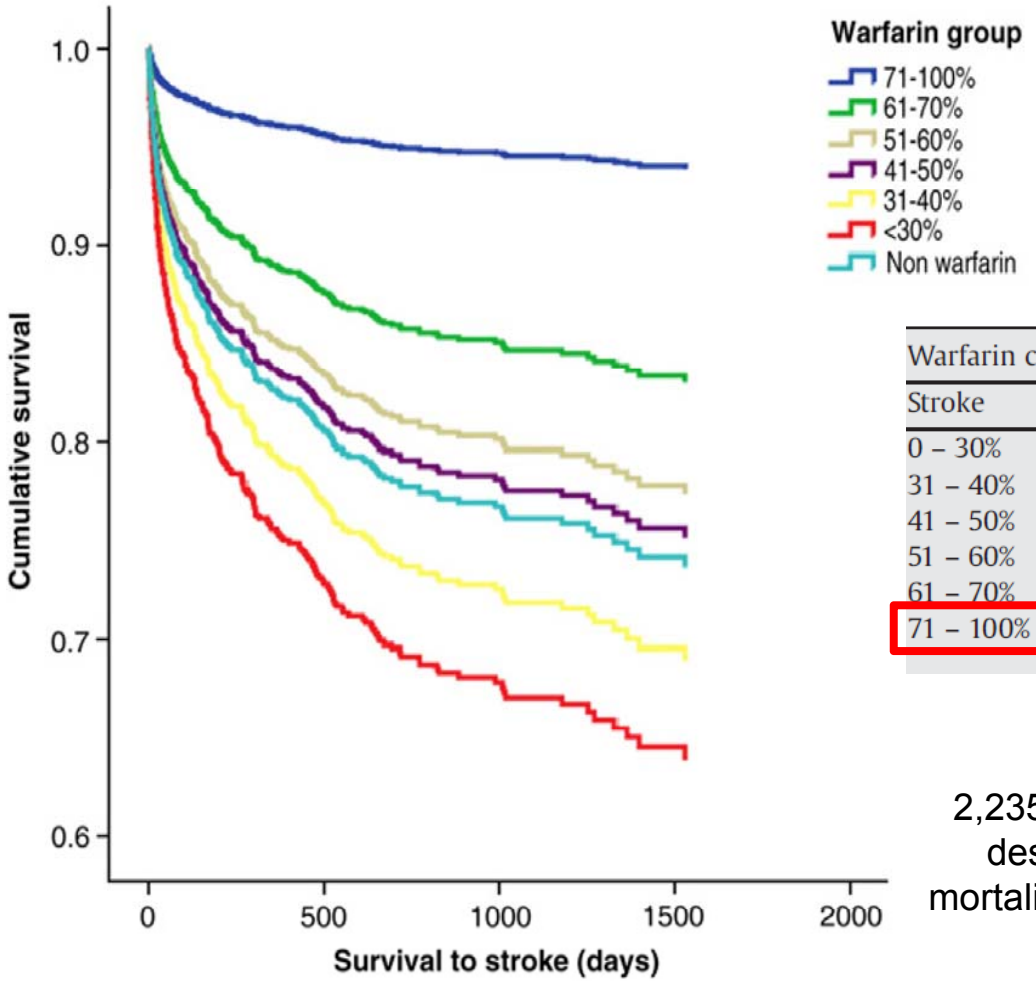
Si calcola con un piccolo programma su un tempo di terapia stabile di almeno 6 mesi.

È complesso da calcolare e (forse) più preciso della **percentuale di controlli in range:**

$$\left[\frac{\text{n.controlli in range}}{\text{n.totale dei controlli}}\right] \times 100$$

Connolly 2008 Circulati

# Qual è il livello minimo di TTR da mantenere per ridurre il rischio di stroke?




| Warfarin control | $CHADS_2$ score ≥2 | | |
|---|---|---|---|
| Stroke | Exp(B) | 95% CI | p |
| 0 – 30% | 1.468 | (0.844-2.551) | 0.174 |
| 31 – 40% | 1.215 | (0.767-1.926) | 0.407 |
| 41 – 50% | 0.933 | (0.628-1.385) | 0.729 |
| 51 – 60% | 0.837 | (0.554-1.265) | 0.399 |
| 61 – 70% | 0.608 | (0.335-1.105) | 0.103 |
| 71 – 100% | 0.203 | (0.050-0.820) | 0.025 |

2,235 NVAF PATIENTS from a retrospective cohort design using linked inpatient, haematology and mortality data from Cardiff and the Vale of Glamorgan, UK

Morgan 2009 Thrombosis Research

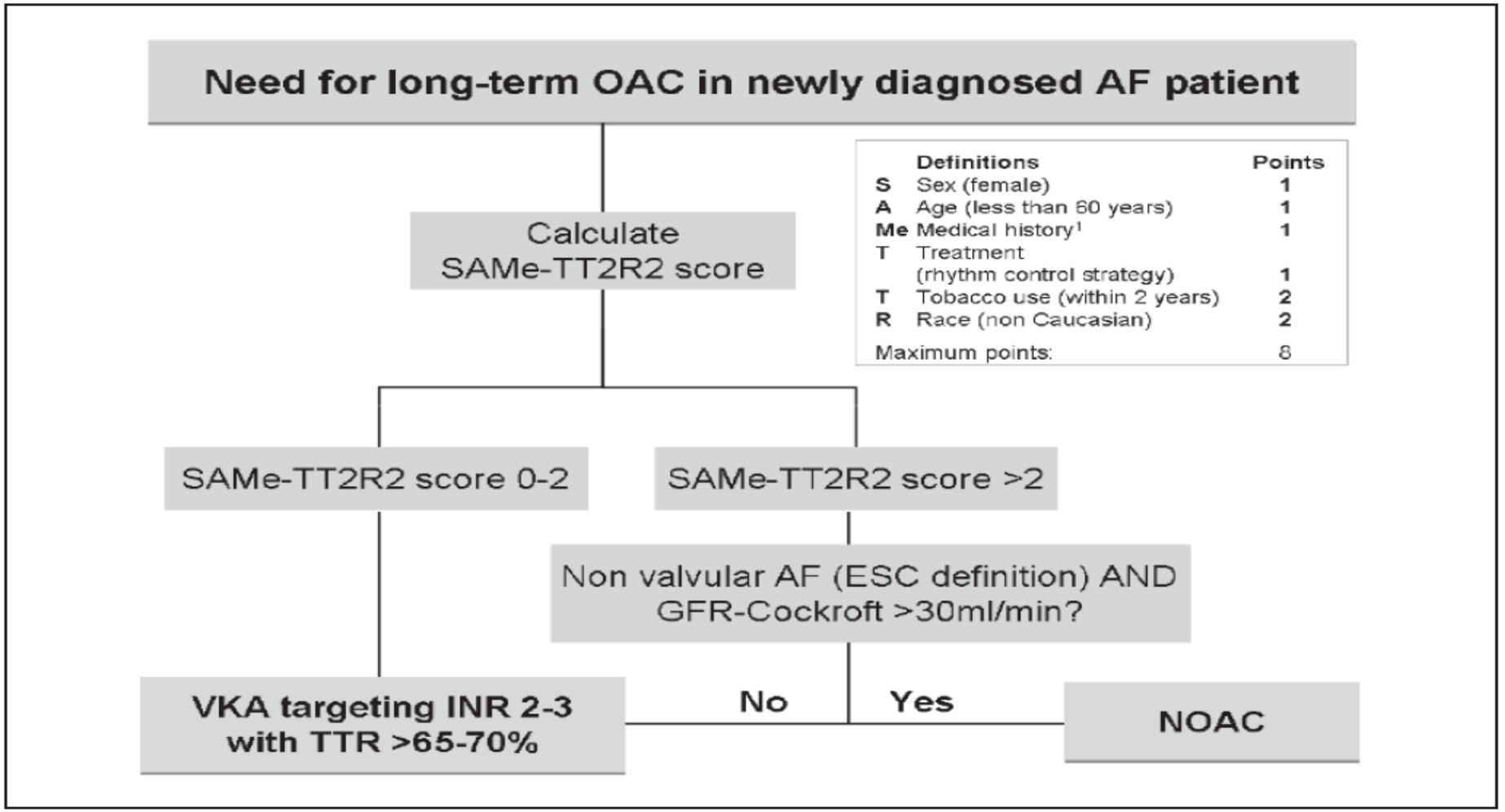
# Possiamo predire la qualità della TAO? Il SAMe-$TT_2R_2$

| | | | |
|---|---|---|---|
| S | Sex (female) | | 1 |
| A | Age (less than 60 years) | | 1 |
| M e | Medical history[1] | Defined as >2 of the following: hypertension, diabetes, CAD/MI, PAD, CHF, previous stroke, pulmonary disease, hepatic or renal disease | 1 |
| T | Treatment (rhythm control strategy) | Defined as patients not treated with beta-blockers or verapamil or treated with amiodarone | 1 |
| T | Tobacco use (within 2 years) | | 2 |
| R | Race (non Caucasian) | **Punteggio max=8** | 2 |

**Bassa performance soprattutto in pazienti anziani**
**Poca praticità**

Lip Chest 2013

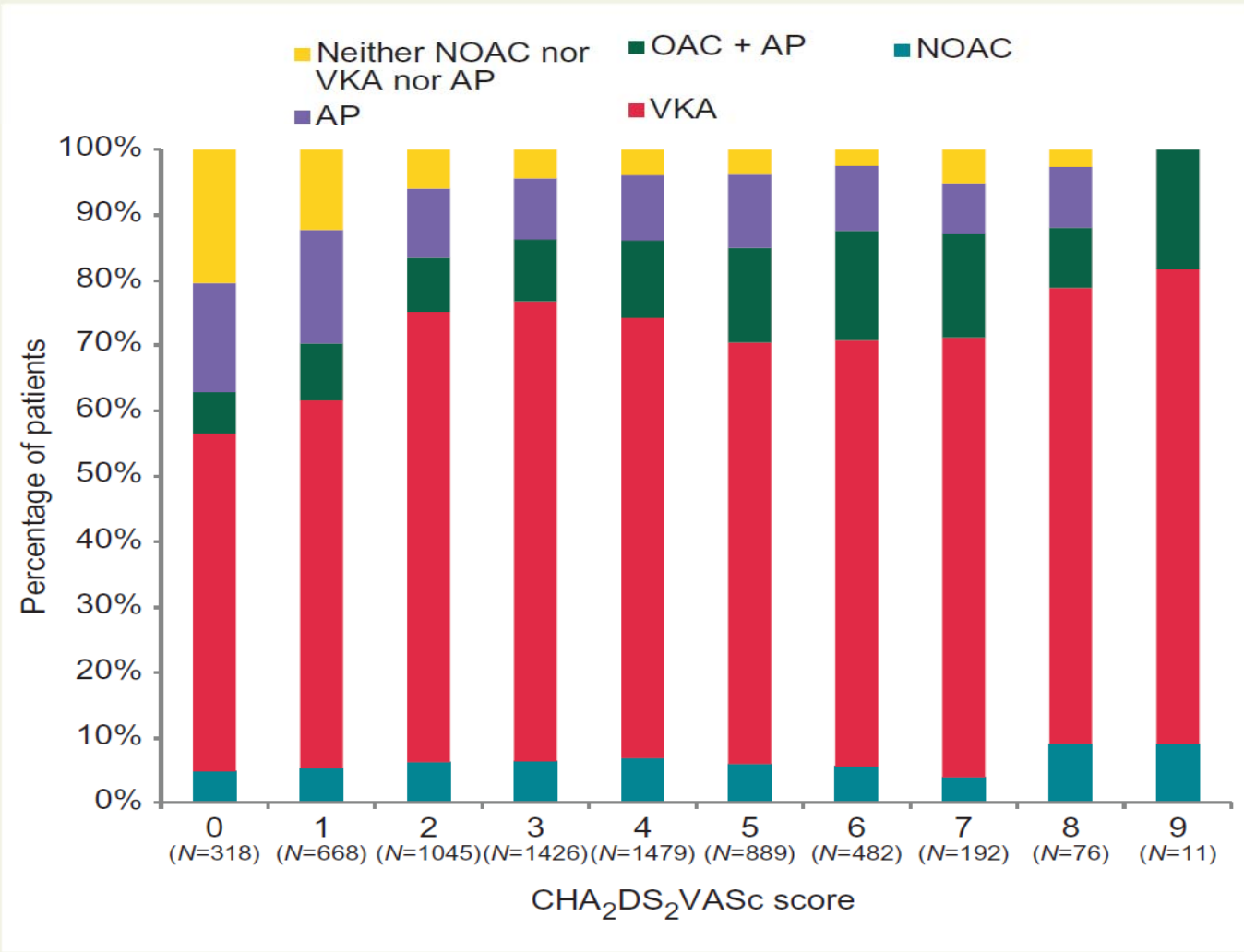
# Il SAMe-$TT_2R_2$ nella scelta della TAO




Fauchier L. TH 2015; 114: 657–659
Lip JAMA. 2015;313(19):1950-1962

# Prescrizione della TAO in Europa in base al rischio di Stroke: studio PREFER in AF

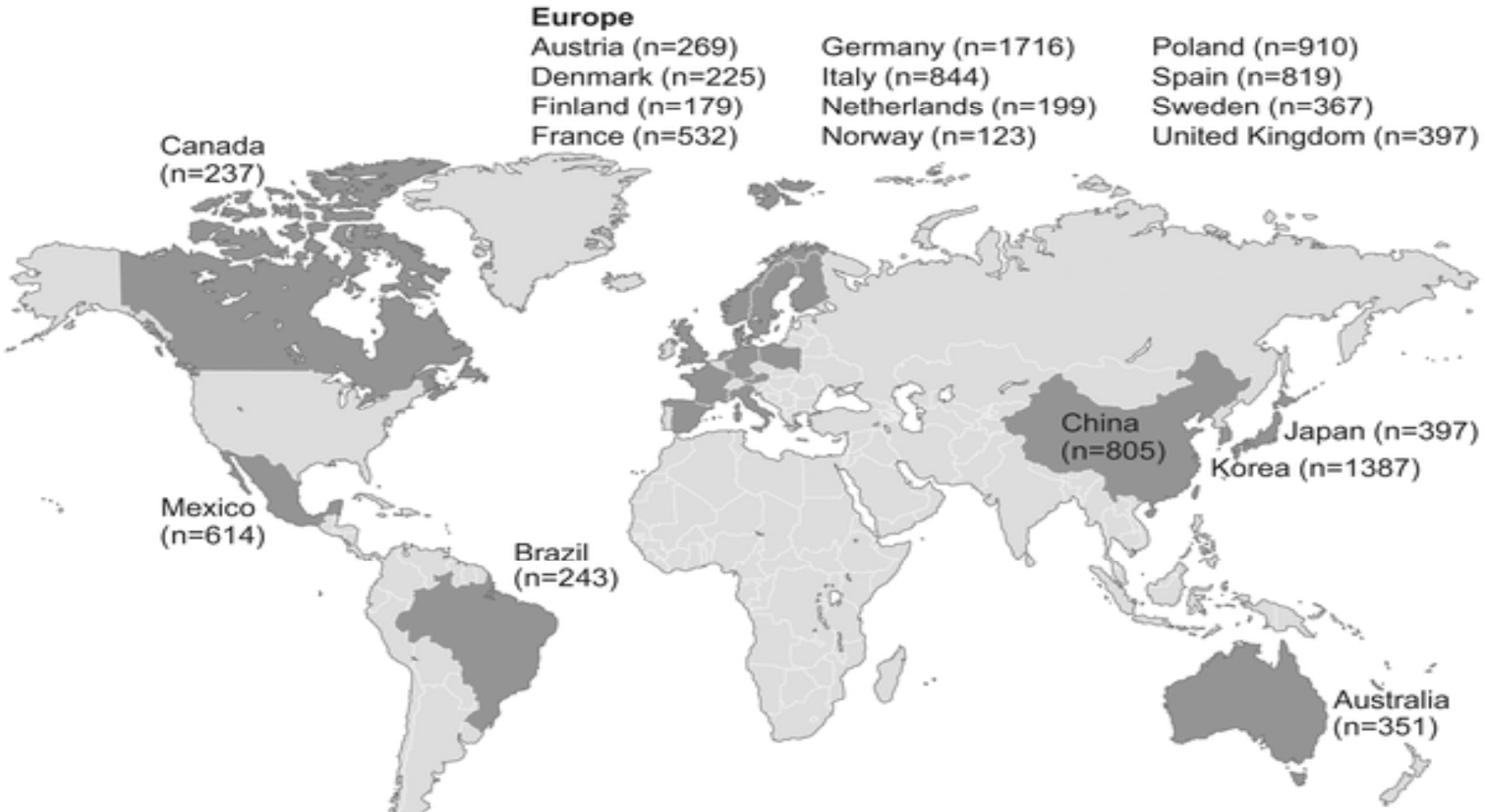
**Uso della terapia antitrombotica in base al rischio di ictus in 7243 pazienti con FA in 7 nazioni europee (**




2014 Europace Kirchhof

# THE GARFIELD REGISTRY

**Figure 1. Number of patients enrolled per country in Cohort 1 (n = 10,614).**




Kakkar AK, Mueller I, Bassand JP, Fitzmaurice DA, Goldhaber SZ, et al. (2013) Risk Profiles and Antithrombotic Treatment of Patients Newly Diagnosed with Atrial Fibrillation at Risk of Stroke: Perspectives from the International, Observational, Prospective GARFIELD Registry. PLoS ONE 8(5): e63479. doi:10.1371/journal.pone.0063479 http://127.0.0.1:8081/plosone/article?id=info:doi/10.1371/journal.pone.0063479

# THE GARFIELD* REGISTRY

TAO

Th. antipiastrinica

**Use of antithrombotic therapies, overall and according to CHA2DS2VASc score**

* Global Anticoagulant Registry in the Field

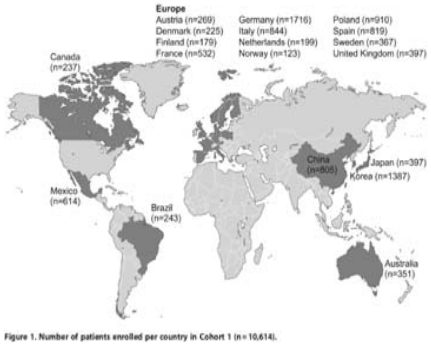
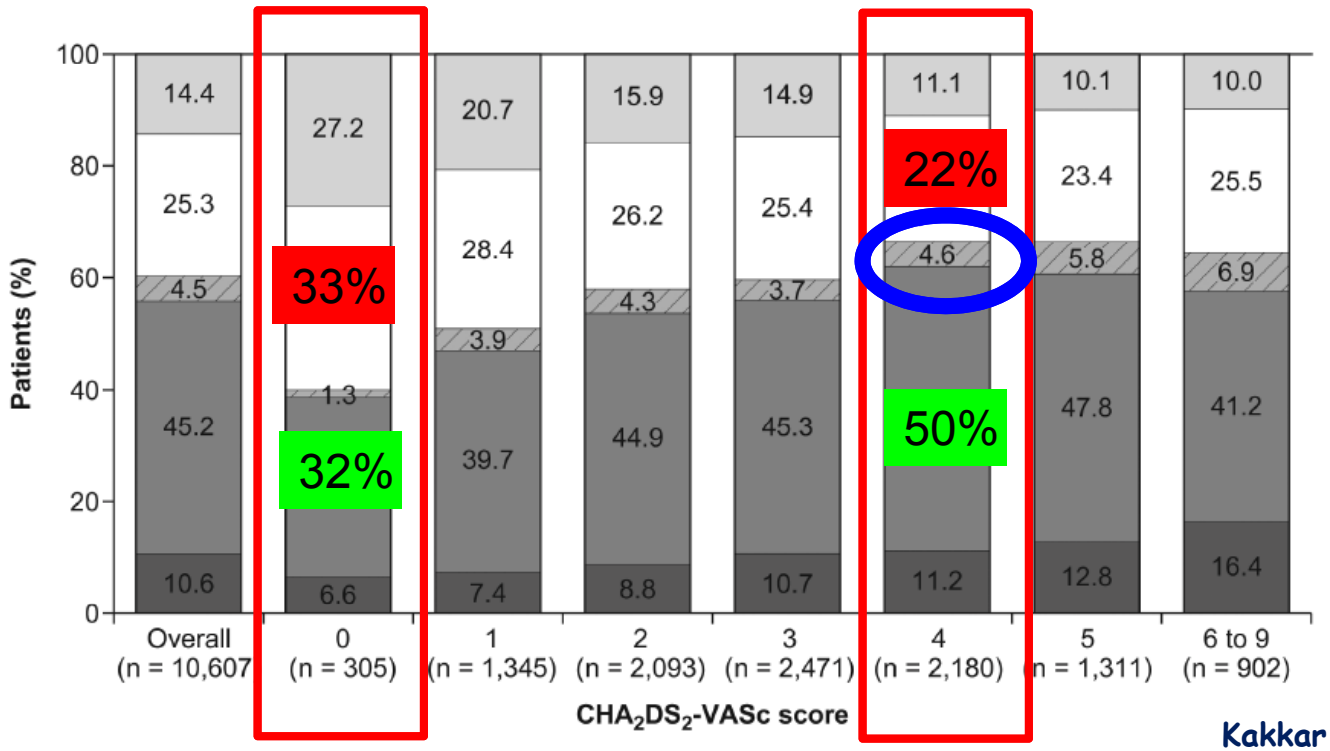
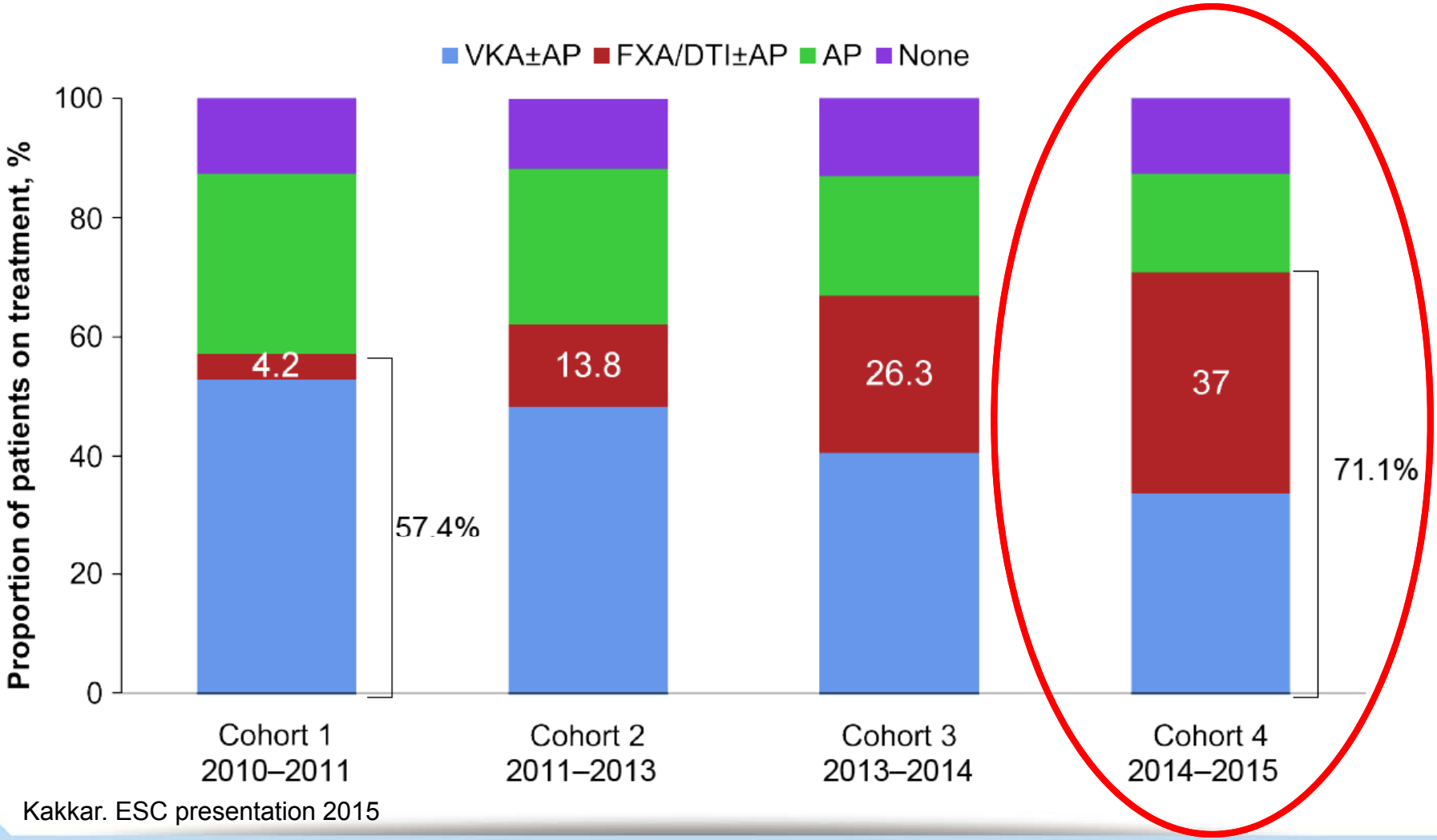


Figure 1. Number of patients enrolled per country in Cohort 1 (n=10,614).




Kakkar et al. PLOS one 2013

# The Garfield registry




Kakkar. ESC presentation 2015

# Expert opinion highlights concern over lack of an Antidote

**Think Tank Meeting hosted by the Cardiac Safety Research Consortium (CSRC) and the FDA on April 22nd 2014**

Christopher Granger, MD, another Duke cardiologist, said **a reversal agent is not necessary to use NOACs safely and effectively, but a reversal agent would improve the uptake of the drugs. The biggest problem is not bleeding "but millions of people out there not being treated ... One of the barriers is lack of a reversal agent."**

The major bleeding rate with warfarin is roughly 3% per year, and it is only slightly lower with NOACs. Granger said. But the real need for a reversal agent is a narrow spectrum of bleeding -- intracranial hemorrhage (ICH) and trauma -- even in those cases reversal agents will be helpful but unlikely to have a major impact. The best option is to prevent ICH. "The new agents cut ICH and hemorrhagic stroke in half, and they, not surprisingly, reduce death," he said.

Moreover, Granger said that when there is a major bleed in a patient on warfarin, a reversal agent (e.g., vitamin K) is used only 10% to 25% of the time, "So even when we have reversal strategies, we just don't use them much in practice."

NOAC = novel oral anticoagulant Peck P. MedPage Today; April 2014:; Accessed July 2014

# TERAPIA ANTICOAGULANTE

- Lo scenario
- I NAO: nuove prospettive
- I NAO: caratteristiche a confronto
- I NAO: profilo di sicurezza

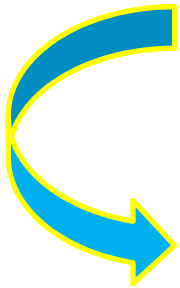
# Limiti superati con i NOAC

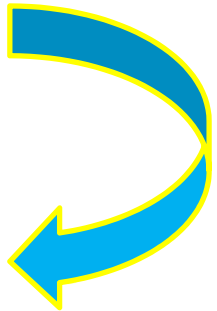
- ~~Risposta imprevedibile~~
- ~~Ristretta finestra terapeutica (INR range 2-3)~~
- ~~Monitoraggio periodico della coagulazione~~

**La terapia con i NOAC presenta numerosi vantaggi che rendono più sicuro l'utilizzo**

- ~~Frequenti aggiustamenti di dose~~
- ~~Numerose interazioni con cibo~~
- LIMITATE interazioni farmacologiche

# Registro PREFER in AF ⟶ ESC 2014





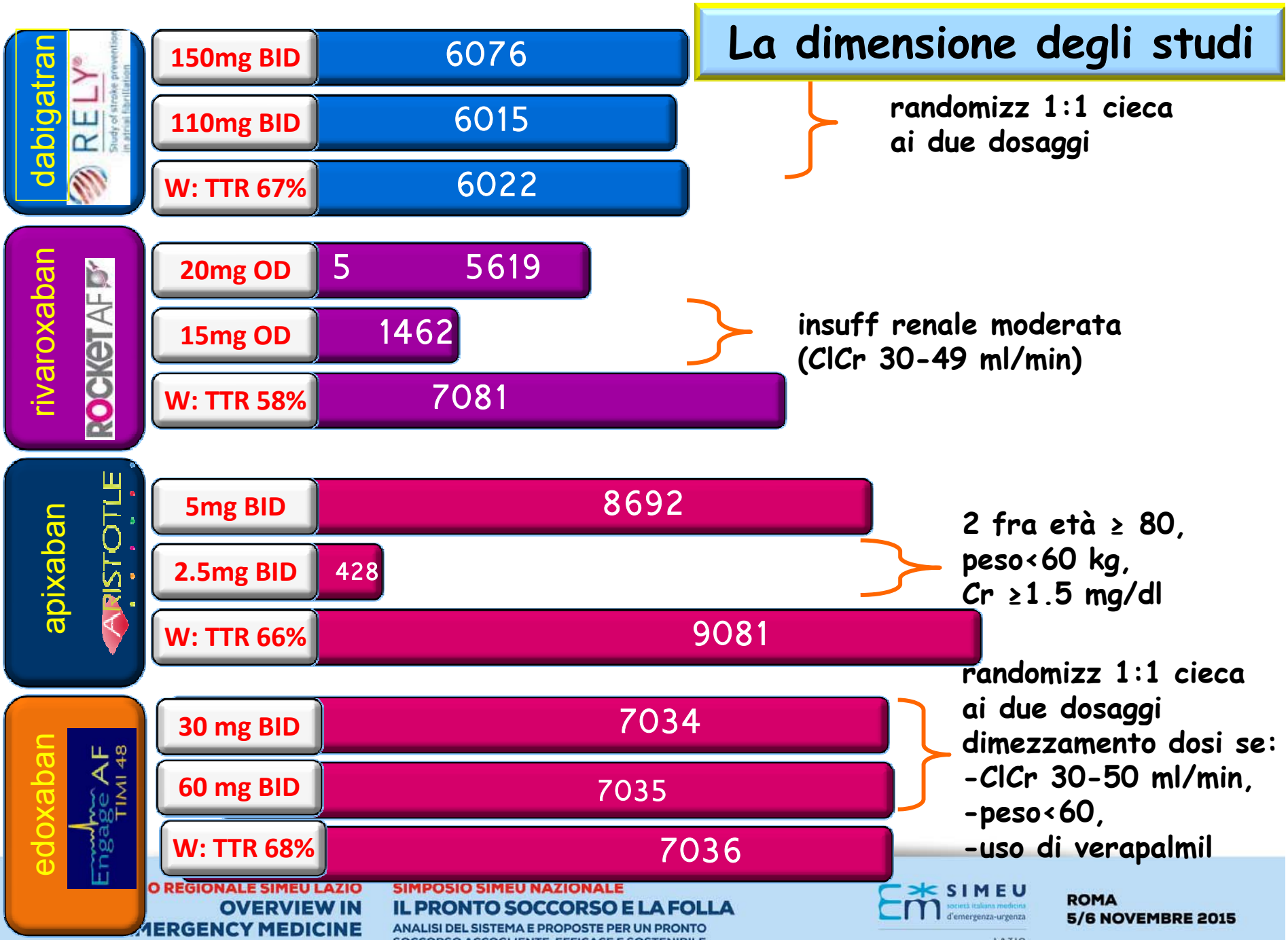
↑ NAO
da 6,1% a 12,6%

↓ AVK
da 66,3 a 61,8%

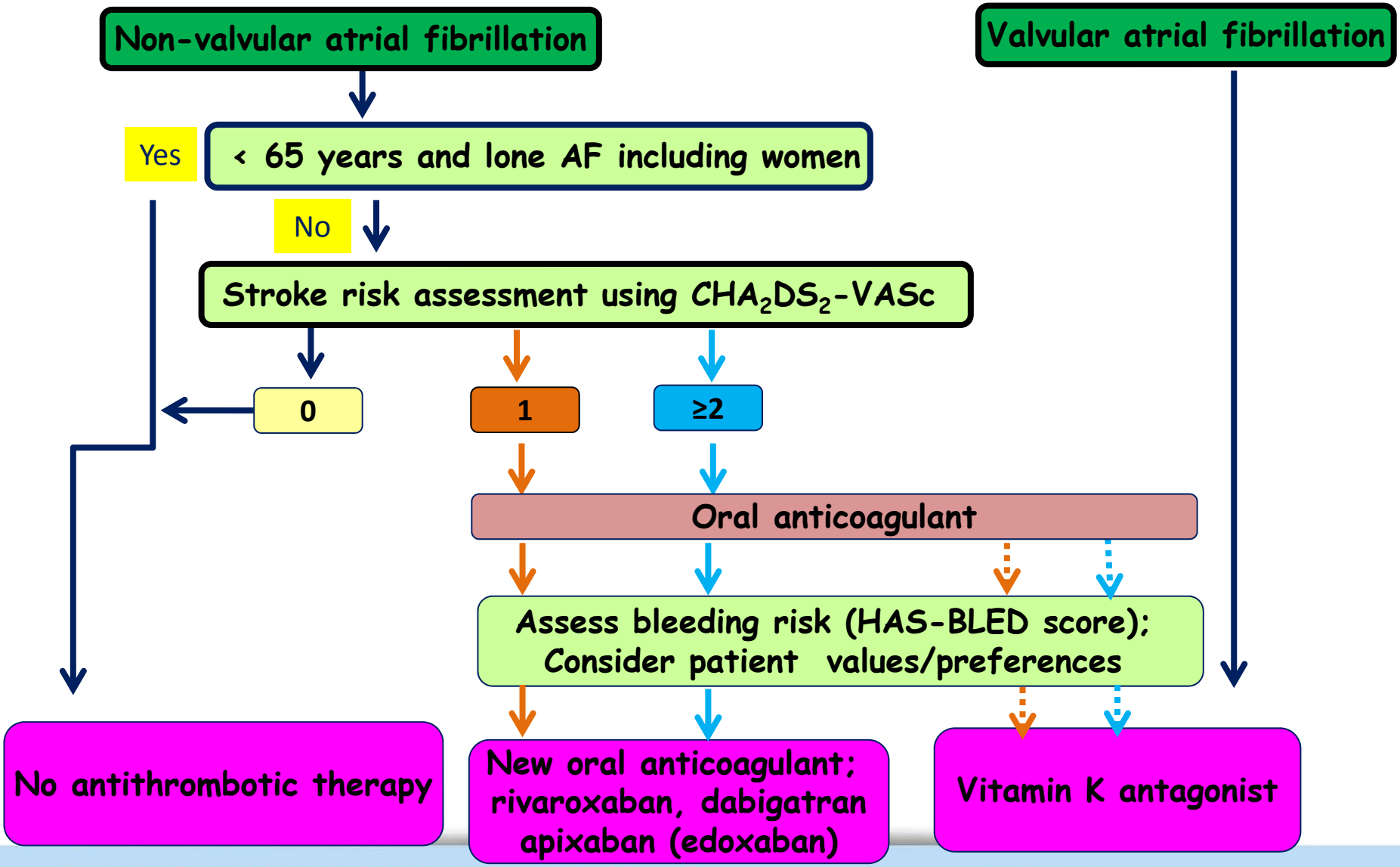
in 1 anno di follow up

https://www.agenziafarmaco.gov.it/registri/

# La dimensione degli studi



# Scelta dell'anticoagulante






Camm AJ *et al. Eur Heart J* 2012

# I NAO sono tutti uguali? Ci sono diversi punti di vista

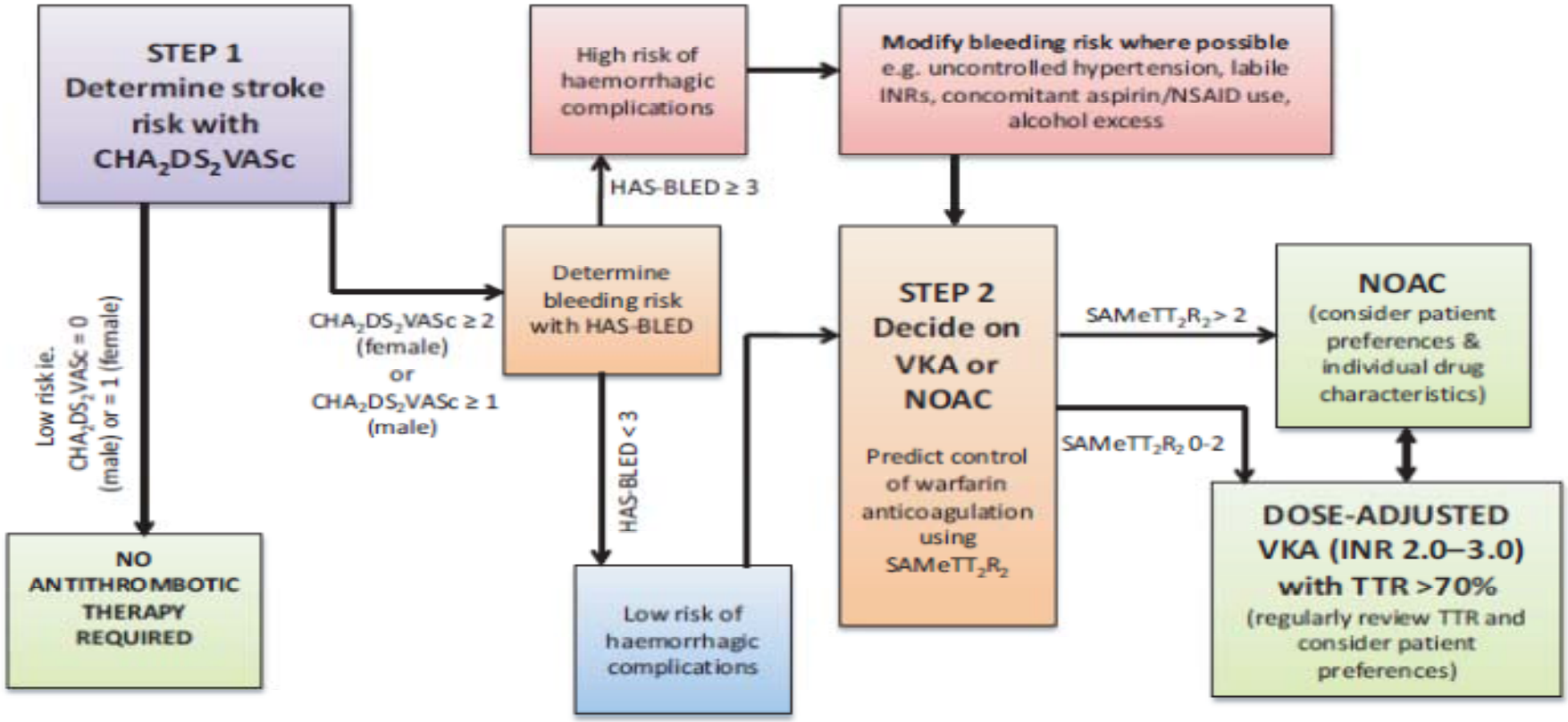
- Le popolazioni studiate nei trial sono diverse e non confrontabili tra loro. E comunque il confronto tra trial non dovrebbe essere utilizzato, quindi i NAO dovrebbero essere considerati tutti uguali come alternativa di successo al Warfarin

MA …

- Si sono registrate differenze tra gli studi relativamente agli outcomes primari
- Il medico dovrebbe scegliere il farmaco in base alle caratteristiche individuali dei pazienti, scegliendo il migliore per quel paziente
- Questo ci porta inevitabilmente a fare dei confronti cross-trial (incluse le network meta-analisi) per cercare di indagare i risultati dei diversi NAO in funzione della tipologia di paziente

# Come prescrivere i NOACs

- Il paziente necessità di trattamento anticoagulante? SI/NO
- Il paziente beneficia della terapia con i NOACs? (basso TTR, scarsa compliance, impossiblità ad eseguire prelievi)
- Il paziente presenta controindicazioni all'uso dei NOACs? (Cl Creat < 30 ml/min, severa anemia, protesi meccaniche valvolari cardiache/stenosi mitralica da moderata a severa)
- Il paziente assume farmaci che possono interferire con la terapia con i NOACs?




Algoritmo

**Fig. 1** *An algorithm for the risk assessment of atrial fibrillation (AF) patients about to start anticoagulation treatment. The assessment of risk of anticoagulation in patients with AF involves the use of the $CHA_2DS_2VASc$, HAS-BLED and $SAMeTT_2R$ scores to evaluate stroke risk, bleeding risk and likelihood of successful warfarin therapy, respectively. Non-vitamin K antagonist oral anticoagulants (NOACs) may be considered where the $SAMeTT_2R$ score predicts poor control of anticoagulation with warfarin. VKA, vitamin K antagonist; INR, international normalized ratio; NSAID, nonsteroidal anti-inflammatory drug; OAC, oral anticoagulant; TTR, time in therapeutic range.*

2015 Shields J Intern Med

# TERAPIA ANTICOAGULANTE

- Lo scenario
- I NAO: nuove prospettive
- I NAO: caratteristiche a confronto
- I NAO: profilo di sicurezza

# I Nuovi Anticoagulanti Orali

1. Sono *clinicamente equivalenti - statisticamente non-inferiori* - al warfarin nella prevenzione delle complicanze cardioemboliche della FA
2. Riducono *in modo clinicamente rilevante - statisticamente significativo* - le complicanze emorragiche maggiori rispetto al warfarin
3. Presentano una maggiore *praticità di impiego* - modeste interazioni farmacologiche e con il cibo, assenza della necessità di controlli continui dell'assetto coagulativo.

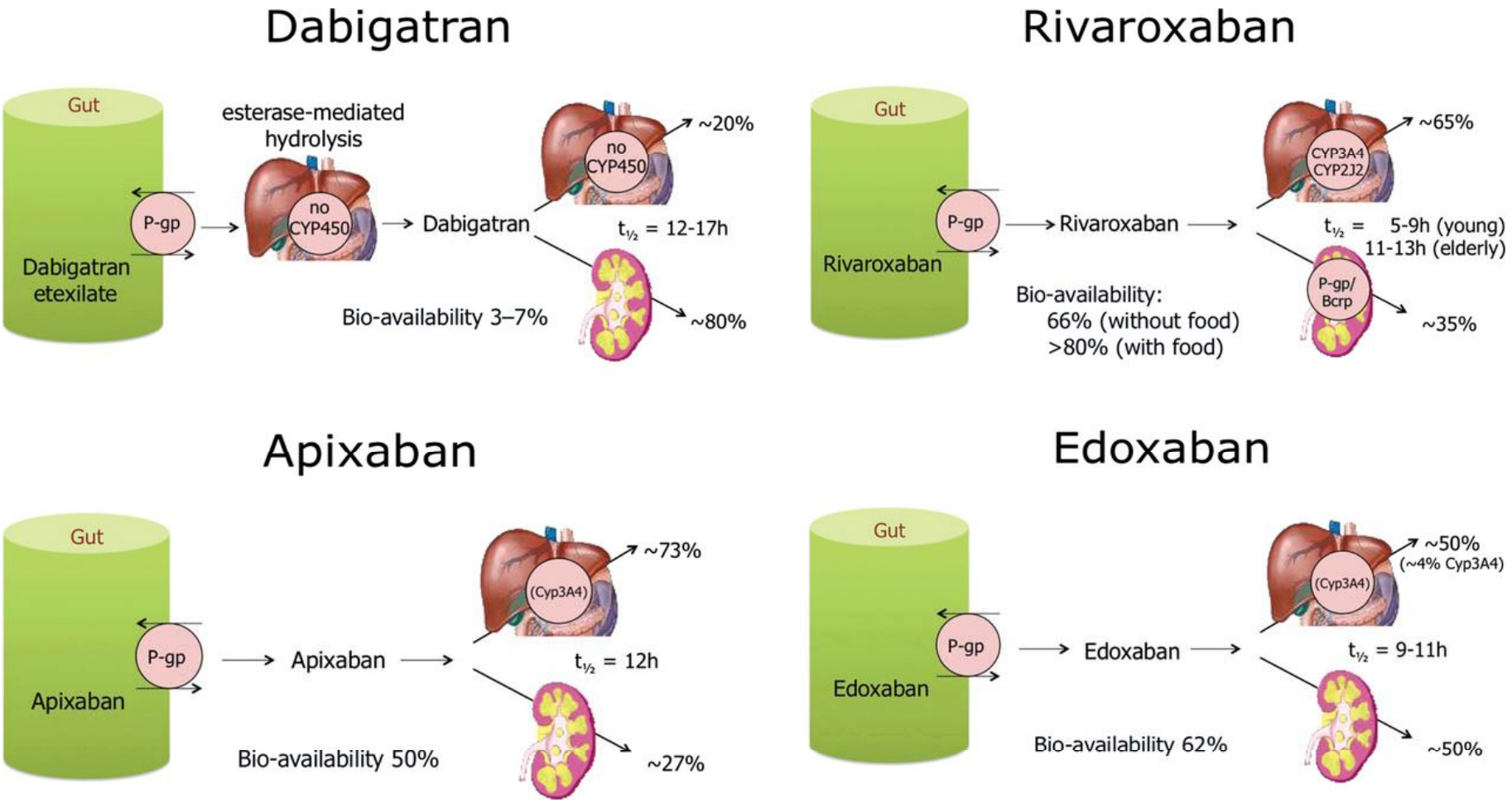
# Vantaggio dei NOACs indipendente dal TTR!!!!

The mean TTRs in the warfarin groups were the following:

– RE-LY trial: 64%[1]
– ROCKET AF trial: 55%[2]
– ARISTOTLE trial: 62%[3]
– ENGAGE AF-TIMI 48 trial: 65%[4]


1. Connolly et al. N Engl J Med. 2009;361:1139–1151;
2. Patel et al. N Engl J Med. 2011;365:883–891;
3. Granger et al. N Engl J Med. 2011;365:981–992;
4. Giugliano et al. N Engl J Med. 2013;369:2093–2104.

# Absorption and metabolism of the different new anticoagulant drugs.






Heidbuchel H et al. Europace 2013;15:625-651

# ABSORPTION AND METABOLISM OF NOAC

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Bioavailability | 3-7% | 50% | 62% | 66% (w/o food)<br>~100% with food |
| Prodrug | yes | no | no | no |
| Clearance: non-renal/renal of adsorbed dose if normal renal function | 20%/80% | 73%/27% | 50%/50% | 65%/35% |
| Liver metabolism: CYP3A4 | no | yes (elimination; minor CYP3A4) | minimal (<4% of elimination) | yes (elimination) |
| Absorption with food | no effect | no effect | 6-22% more | +39% |
| Intake with food? | no | no | no official recommendation yet | mandatory |
| Absorption with H2B/PPI | plasma level -12 to -30% | no effect | no effect | no effect |
| Asian ethnicity | plasma level +25% | no effect | no effect | no effect |
| GI tolerability | dyspepsia 5-10% | no problem | no problem | no problem |
| Elimination half-life | 12-17h | 12h | 9-11h | 5-9h (young)/11-13h (elderly) |

# Possible drug-drug interactions –Ddis
# Effect on NOAC plasma levels
# Three levels of alert:

www.escardio.org/EHRA

| | Interaction | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| Fluconazole | CYP3A4 | no data | no data | no data | +42% |
| Cyclosporin; tacrolimus | P-gp | no data | no data | no data | +50% |
| Clarithromycin; erythromycin | P-gp/ CYP3A4 | +15–20% | no data | no data | +30–54% |
| **HIV protease inhibitors** | P-gp and BCRP/ CYP3A4 | no data | strong increase | no data | up to +153% |
| Rifampicin; St John's wort; **carbamezepine;** phenytoin; **phenobarbital** | P-gp and BCRP/ CYP3A4/CYP2J2 | -66% | -54% | -35% | up to -50% |
| Antacids | GI absorption | -12-30% | no data | no effect | no effect |

**Red** – contraindicated; **orange** – reduce dose D da 150 a 110 mg BID, R da 20 a 15 mg OD, A da 5 a 2,5 mg BID; **yellow** – consider dose reduction if another yellow factor present;
White – no data available, NOA not recommended;
Recommendation made from pharmacokinetic considerations

# Fattori che influenzano i livelli plasmatici dei NOACs

| | | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|---|
| Aged ≥ 80 years | Increased plasma level | | | no data | |
| Aged ≥ 75 years | Increased plasma level | | | no data | |
| Weight ≤ 60 kg | Increased plasma level | | | | |
| Renal function | Increased plasma level | | | | |

Altri fattori che aumentano il rischio di sanguinamento

Interazioni farmacodinamiche – antipiastrinici, FANS,
Terapia steroidea sistemica
Altri anticoagulanti
Chirurgia recente su organi critici (cervello, occhio)
Trombocitopenia (i.e chemioterapia)
HAS-BLED ≥ 3

**Orange** – reduce dose; **yellow** – consider dose reduction if another yellow factor present; **hatching** – no data available;
**Recommendation made from pharmacokinetic considerations**

**Table 7** Estimated drug half lives and effect on AUC NOAC plasma concentrations in different stages of CKD compared to healthy controls

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| CrCl >80 mL/min | 12–17 h[61] | 12 h | 10–14 h[51,65] | 5–9 h (young)<br>11–13 h (elderly) |
| CrCl 50–80 mL/min | ~17 h[122] | ~14.6 h[123] | ~8.6 h[124] | ~8.7 h[125] |
| CKD Stages I and II | (+50%) | (+16%) | (+32%)[SmPC] | (+44%)[126] |
| CrCl 30–50 mL/min | ~19 h[122] | ~17.6 h | ~9.4 h[124] | ~9.0 h |
| CKD Stage III | (+320%) | (+29%) | (+74%)[SmPC] | (+52%)[126] |
| CrCl 15–30 mL/min | ~28 h[122] | ~17.3 h | ~16.9 h[124] | ~9.5 h |
| CKD Stage IV | (+530%) | (+44%) | (72%)[SmPC] | (+64%)[126] |
| CrCl ≤ 15 mL/min | No data | – | – | – |
| CKD Stage V; off-dialysis | | (+36%) | (+93%)[SmPC] | (+70%)[127] |

CKD, chronic kidney disease; CrCl, creatinine clearance.

# GESTIONE DOSAGGI

| | Apixaban | Rivaroxaban | Dabigatran |
|---|---|---|---|
| **Recommended daily dose** | 5 mg bd | 20 mg od | 150 mg bd |
| **Dose reduction** | 2.5 mg bd | 15 mg od | 110 mg bd |
| | If ≥2 of the following:<br><br>•Age ≥ 80 years<br>•Body weight ≤ 60 kg<br>•Serum creatinine ≥1.5 mg/dL (133 µmol/L) | In patients with:<br><br>•Moderate (CrCl: 30-49 mL/min) | Recommended:<br><br>•Age ≥ 80 yrs<br>•Increased bleeding risk and<br>- Excessive dabigatran exposure<br>- CrCl 30-50 mL/min<br>•Concomitant use of verapamil<br>•Subjects with gastritis, esophagitis, or gastroesophageal reflux |
| | NOT RECOMMENDED<br><br>(CrCl:15-29 mL/min) | NOT RECOMMENDED<br><br>(CrCl: 15-29 mL/min) | |
| | DO NOT USE<br><br>(CrCl:≤ 15 mL/min) | DO NOT USE<br><br>(CrCl:≤ 15 mL/min) | At the discretion of the physician:<br>•Age between 75-80 yrs<br>•Increased bleeding risk<br><br>DO NOT USE<br>(CrCl: 15-29 mL/min) |

# Measuring the anticoagulant effect of NOACs

| | Dabigatran | Apixaban | Edoxaban | Rivaroxaban |
|---|---|---|---|---|
| Plasma peak | 2h after ingestion | 1-4h post ingestion | 1-2h after ingestion | 2-4h after ingestion |
| Plasma trough | 12-24h after ingestion | 12-24h after ingestion | 12-24h after ingestion | 16-24h after ingestion |
| PT | cannot be used | cannot be used | prolonged but no known relation with bleeding risk | prolonged: may indicate excess bleeding risk but local calibration required |
| INR | cannot be used | cannot be used | cannot be used | cannot be used |
| aPTT | at trough >2x ULN suggests excess bleeding risk | cannot be used | prolonged but no known relation with bleeding risk | cannot be used |
| dTT | At trough >200ng/ml ≥ 65s: excess bleeding risk | cannot be used | cannot be used | cannot be used |
| Anti-FXa assays | n/a | quantitative; no data on threshold values for bleeding or thrombosis | quantitative; no data on threshold values for bleeding or thrombosis | quantitative; no data on threshold values for bleeding or thrombosis |
| Ecarin clotting time | at trough >2x ULN: excess bleeding risk | not affected; cannot be used | not affected; cannot be used | not affected; cannot be used |

# I NAO sono tutti uguali? Parametri da considerare

- **Efficacia nella riduzione dell'ictus**
- **Sicurezza**
  - Sanguinamenti Fatali/Maggiori
  - Sanguinamenti Gastrointestinali
- **Mortalità**
- **Maneggevolezza**
  - Aderenza e persistenza
  - Facilità nella gestione del paziente
- **Ma anche…**
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - Cosa ci dicono i primi dati di Real Life dei NAO?

# I NAO sono tutti uguali? Parametri da considerare

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- **Sicurezza**
  - Sanguinamenti Maggiori
  - Sanguinamenti Gastrointestinali
- **Mortalità**
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- **Ma anche…**
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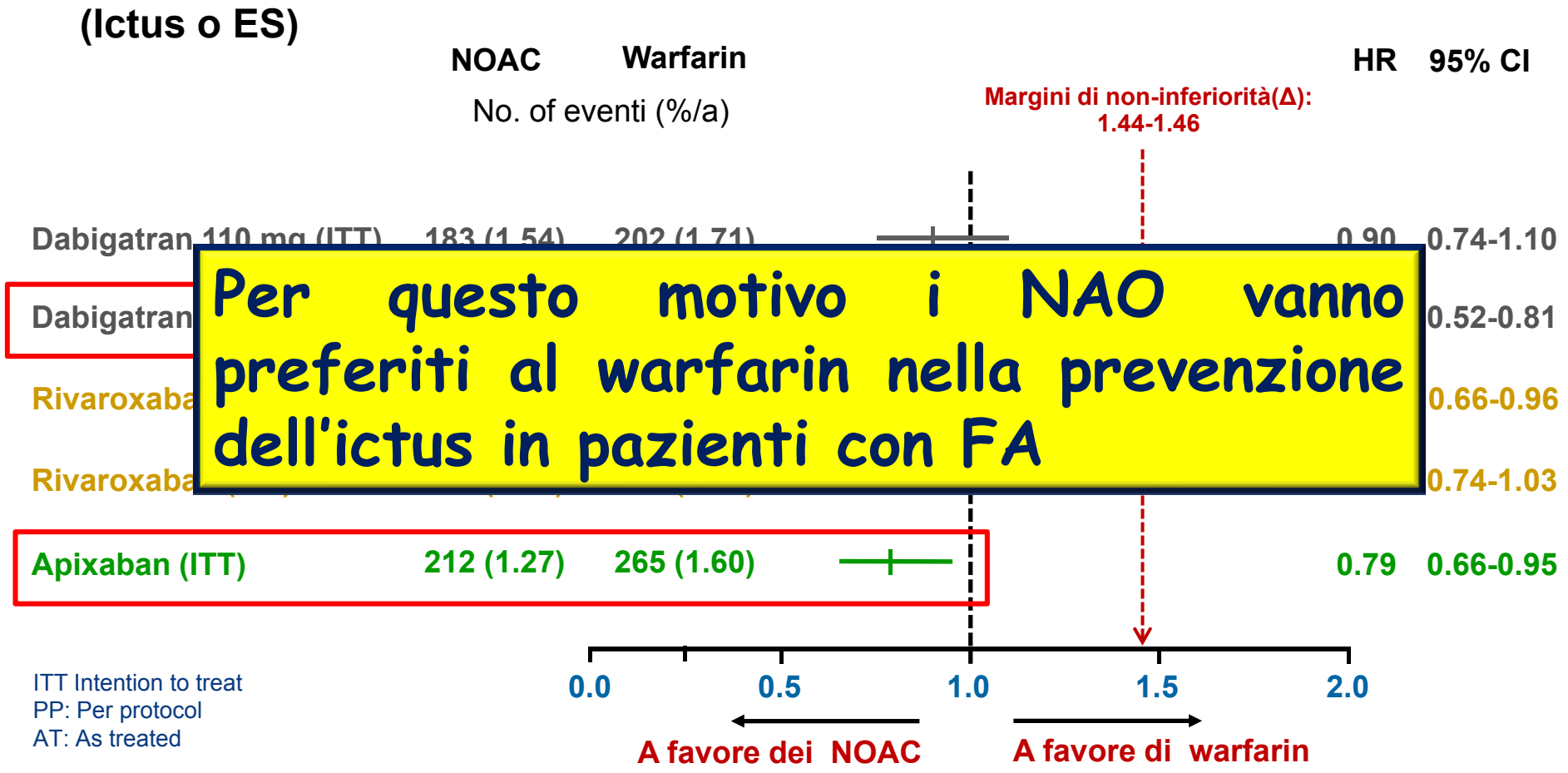
  - Cosa ci dicono i primi dati di Real Life dei NAO?

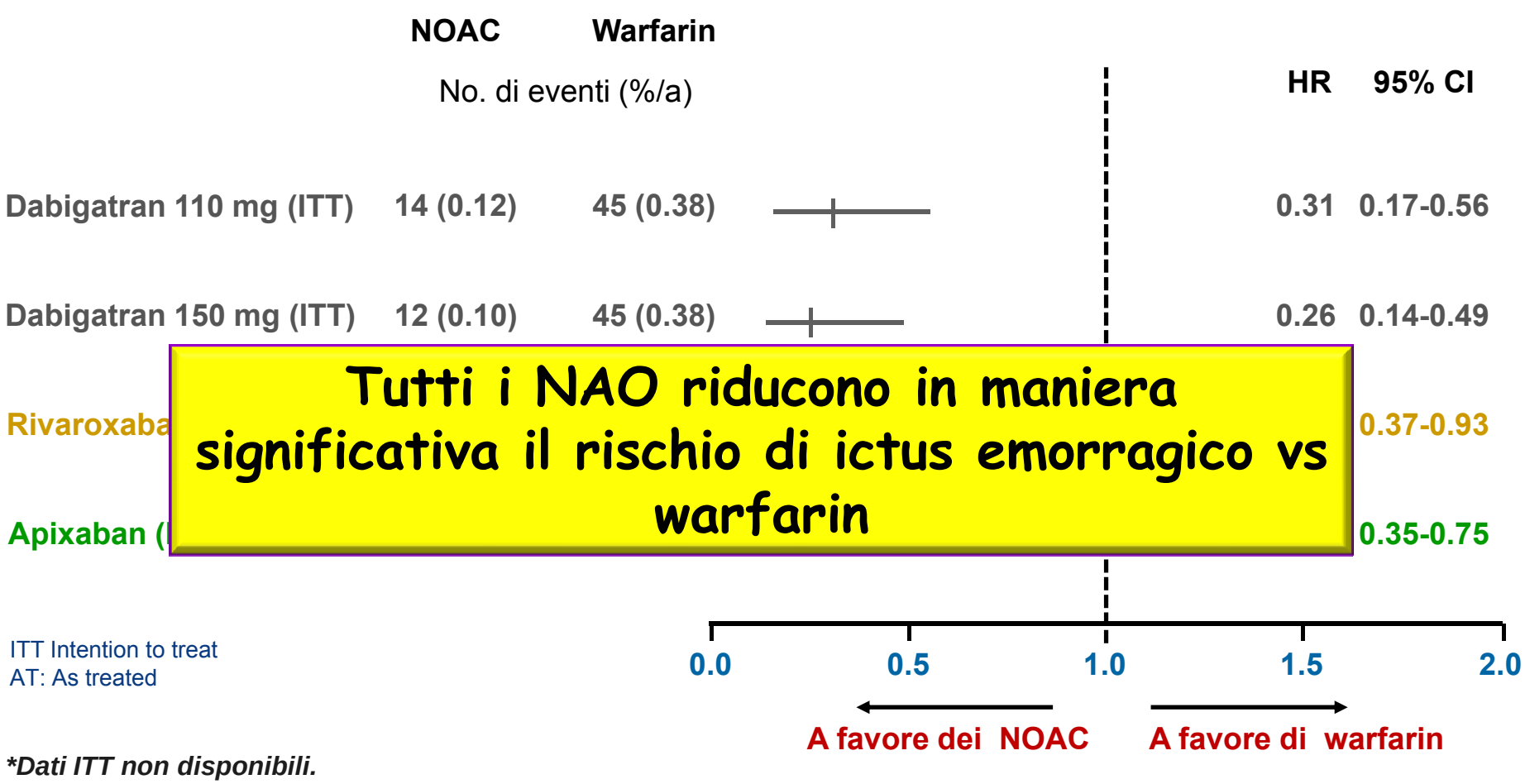
# NOAC *vs.* warfarin: outcome primario di efficacia





1. Connolly et al. NEJM 2010;363:1875-6. 2. Patel et al. NEJM 2011;365:883-91.
3. Granger et al. NEJM 2011;365:981-92. 4. Rivaroxaban SmPC 2012

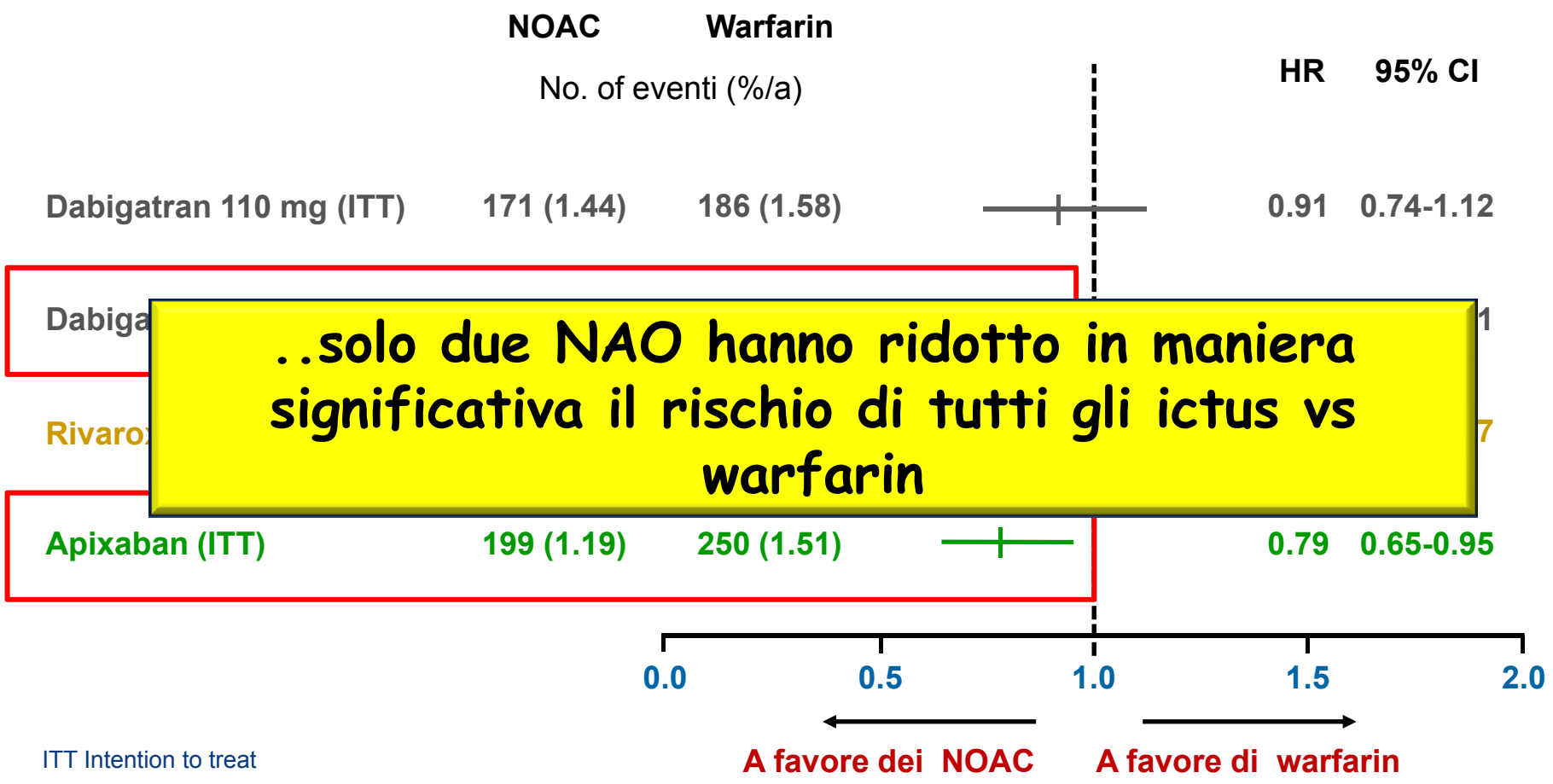
# NOAC *vs.* warfarin: ictus emorragico




***Dati ITT non disponibili.**

. Connolly et al. NEJM 2010;363:1875-6, suppl app. 2. Patel et al. NEJM 2011;365:883-91,suppl app. 3. Granger et al. NEJM 2011;365:981-92.

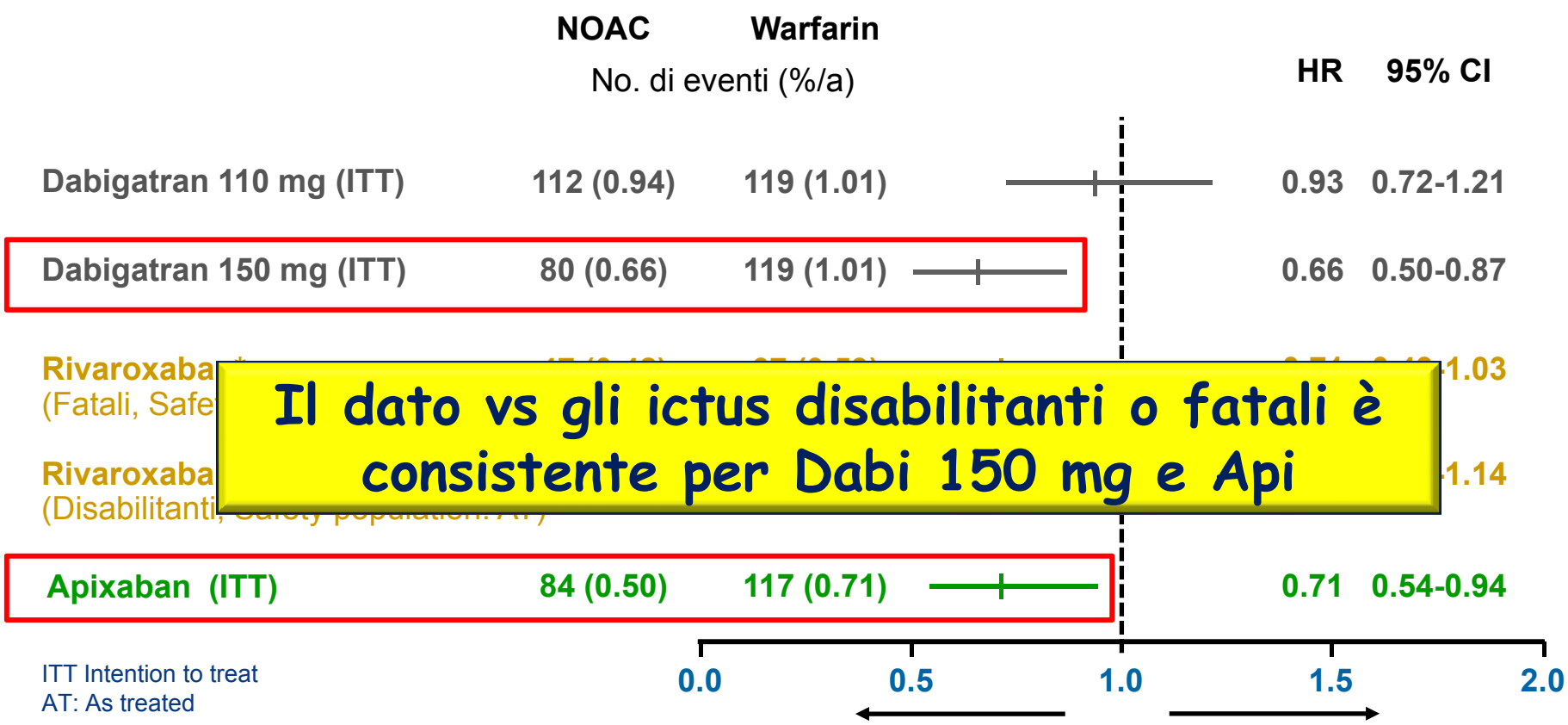
# NOAC *vs.* warfarin: tutti gli ictus




ITT Intention to treat

. Connolly et al. NEJM 2010;363:1875-6. 2. Rivaroxaban SmPC 2012 3. Granger et al. NEJM 2011;365:981-92.

# NOAC *vs.* warfarin: ictus disabilitanti o fatali




**Il dato vs gli ictus disabilitanti o fatali è consistente per Dabi 150 mg e Api**

***Dati ITT non disponibili.**

. Connolly et al. NEJM 2010;363:1875-6, suppl app. 2. Patel et al. NEJM 2011;365:883-91,suppl app. 3. Granger et al. NEJM 2011;365:981-92.

# I NAO sono tutti uguali? Parametri da considerare

- Efficacia nella riduzione dell'ictus
- **Sicurezza**
  - **Sanguinamenti Maggiori**
  - **Sanguinamenti Gastrointestinali**
- Mortalità
- Maneggevolezza
  - Aderenza e persistenza
  - Facilità nella gestione del paziente
- Ma anche…
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - Cosa ci dicono i primi dati di Real Life dei NAO?

# TERAPIA ANTICOAGULANTE

- Lo scenario
- I NAO: nuove prospettive
- I NAO: caratteristiche a confronto
- I NAO: profilo di sicurezza

# Il bleeding intracranico si verifica anche in soggetti in range terapeutico.

| | Patient-years of follow-up | Bleeding | | | ×100 patient-years | Relative risk (95% CI) |
|---|---|---|---|---|---|---|
| | | Fatal | Major | Minor | | |
| **Sex** | | | | | | |
| Female | 874 | 4 | 10 | 61 | 8·6 | 1·25 (0·91–1·71) |
| Male | 1137 | 1 | 13 | 64 | 6·8 | |
| **Age (years)** | | | | | | |
| <50 | 288 | 0 | 0 | 20 | 6·9 | |
| 50–69 | 997 | 0 | 7 | 50 | 5·7 | |
| ⩾70 | 726 | 5 | 16 | 55 | 10·5 | |
| Relative risk ⩾70 *vs* 70 | | | | | | 1·75 (1·28–2·39, p<0·001) |
| **Indication** | | | | | | |
| Ven | | | | | | |
| Arte | | | | | | |
| All | | | | | | |
| Rela | | | | | | |
| **Cen** | | | | | | |
| <10 | | | | | | |
| >10 | | | | | | |
| **Cou** | | | | | | |
| Ace | | | | | | |
| Warfarin | 1258 | 3 | 16 | 67 | 6·8 | |
| **Target INR** | | | | | | |
| ⩽2·8 | 1381 | 3 | 17 | 94 | 8·2 | 0·75 (1·08–0·52) |
| >2·8 | 630 | 2 | 6 | 31 | 6·2 | |
| **Temporally related INR (not available)** | | 2 | 1 | 2 | | |
| <2 | 377 | 0 | 6 | 23 | 7·7 | |
| 2–2·9 | 1116 | 1 | 8 | 45 | 4·8 | |
| 3–4·4 | 442 | 2 | 3 | 37 | 9·5 | |
| 4·5–6·9 | 42 | 0 | 2 | 15 | 40·5 | |
| ⩾7 | 3 | 0 | 3 | 3 | 200 | |
| Relative risk values ⩾4·5 *vs* <4·5 | | | | | | 7·91 (5·44–11·5, p<0·0001) |
| **Timing of events (days)** | | | | | | |
| ⩽90 | 566 | 1 | 9 | 52 | 11·0 | |
| >90 | 1445 | 4 | 14 | 73 | 6·3 | |
| Relative risk ⩽90 *vs* >90 | | | | | | 1·75 (1·27–2·44, p<0·001) |

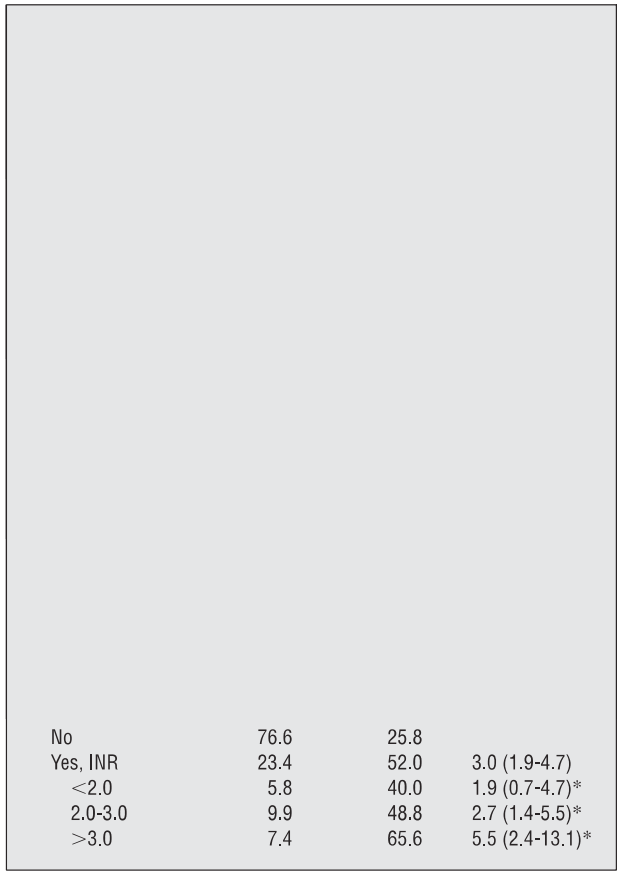
**A fifth of the bleeding events occurred at low anticoagulation intensity (INR < 2, rate 7·7 per 100 patient-years of follow-up).**

**Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT)**

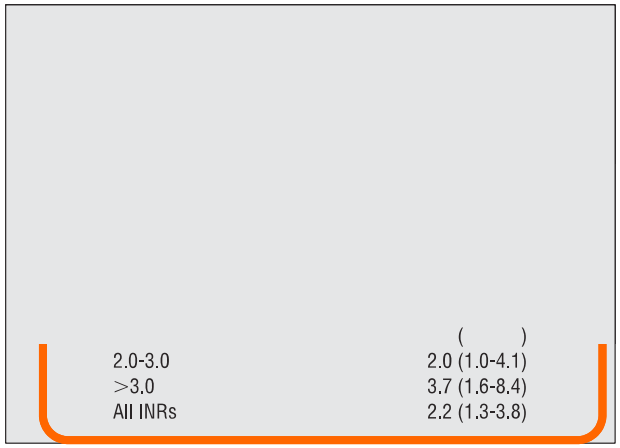
*Gualtiero Palareti, Nicoletta Leali, Sergio Coccheri, Mario Poggi, Cesare Manotti, Armando D'Angelo, Vittorio Pengo, Nicoletta Erba, Marco Moia, Nicola Ciavarella, Gianluigi Devoto, Mauro Berrettini, Serena Musolesi, on behalf of the Italian Study on Complications of Oral Anticoagulant Therapy**

Vol 348 • August 17, 1996

# Il trattamento con Warfarin si associa ad un significativo aumento della mortalità in pazienti colpiti da sanguinamento intracranico



| | | | |
|---|---|---|---|
| No | 76.6 | 25.8 | |
| Yes, INR | 23.4 | 52.0 | 3.0 (1.9-4.7) |
| <2.0 | 5.8 | 40.0 | 1.9 (0.7-4.7)* |
| 2.0-3.0 | 9.9 | 48.8 | 2.7 (1.4-5.5)* |
| >3.0 | 7.4 | 65.6 | 5.5 (2.4-13.1)* |



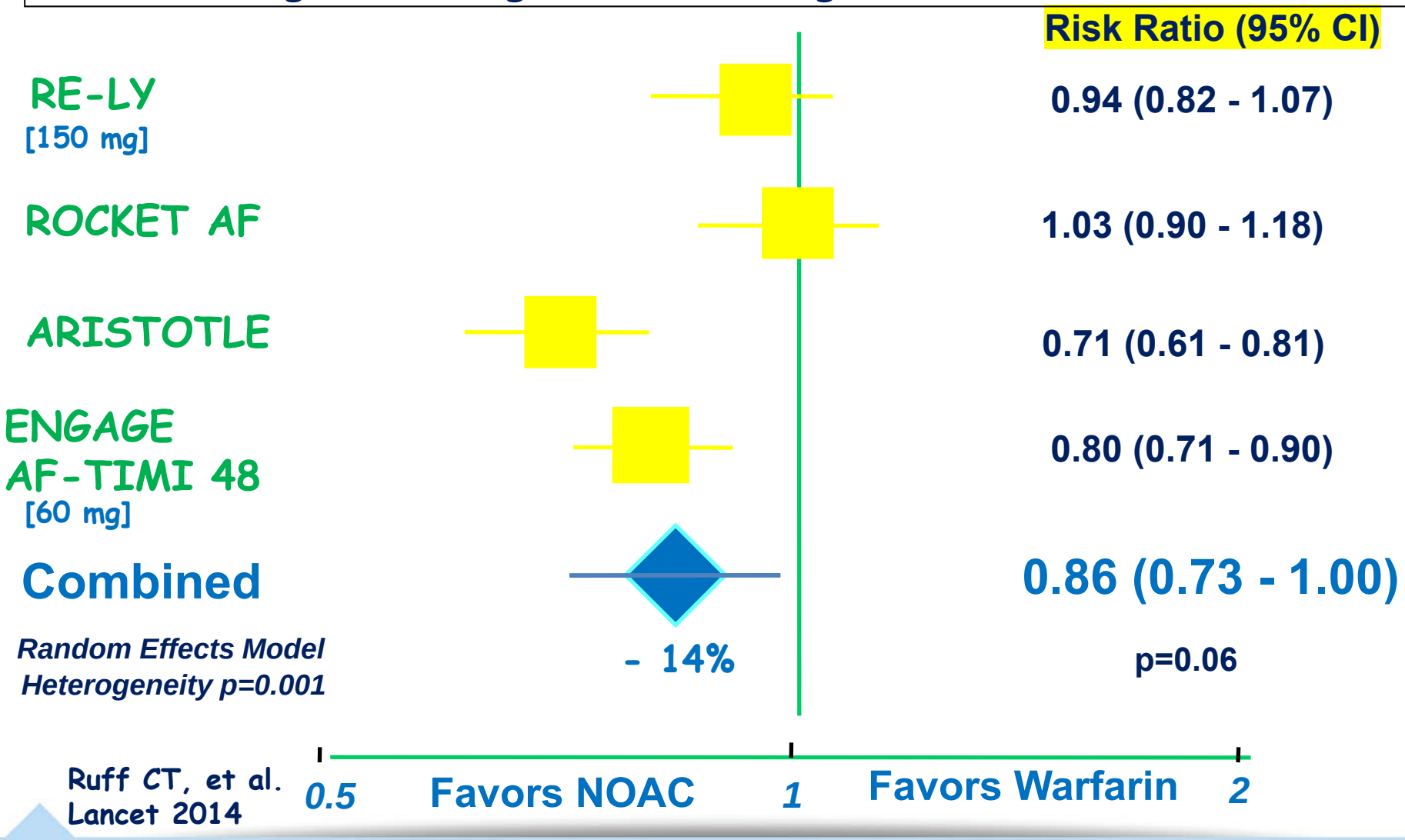
| | |
|---|---|
| | ( ) |
| 2.0-3.0 | 2.0 (1.0-4.1) |
| >3.0 | 3.7 (1.6-8.4) |
| All INRs | 2.2 (1.3-3.8) |

## The Effect of Warfarin and Intensity of Anticoagulation on Outcome of Intracerebral Hemorrhage

*Jonathan Rosand, MD; Mark H. Eckman, MD; Katherine A. Knudsen, BA; Daniel E. Singer, MD; Steven M. Greenberg, MD, PhD*

# All NOACs: Major Bleedings

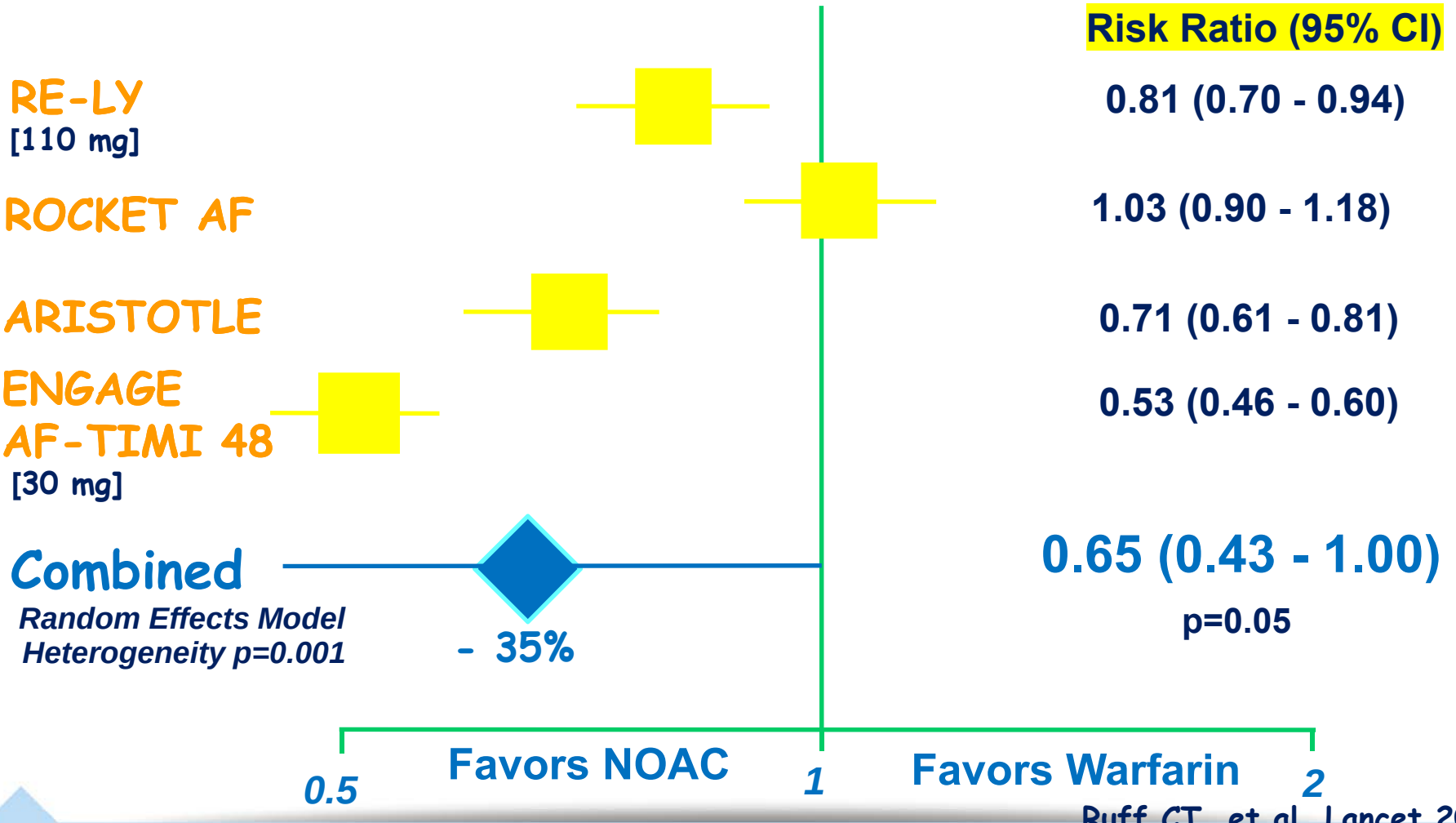
## 'High dose' regimens for dabigatran and edoxaban




Ruff CT, et al. Lancet 2014

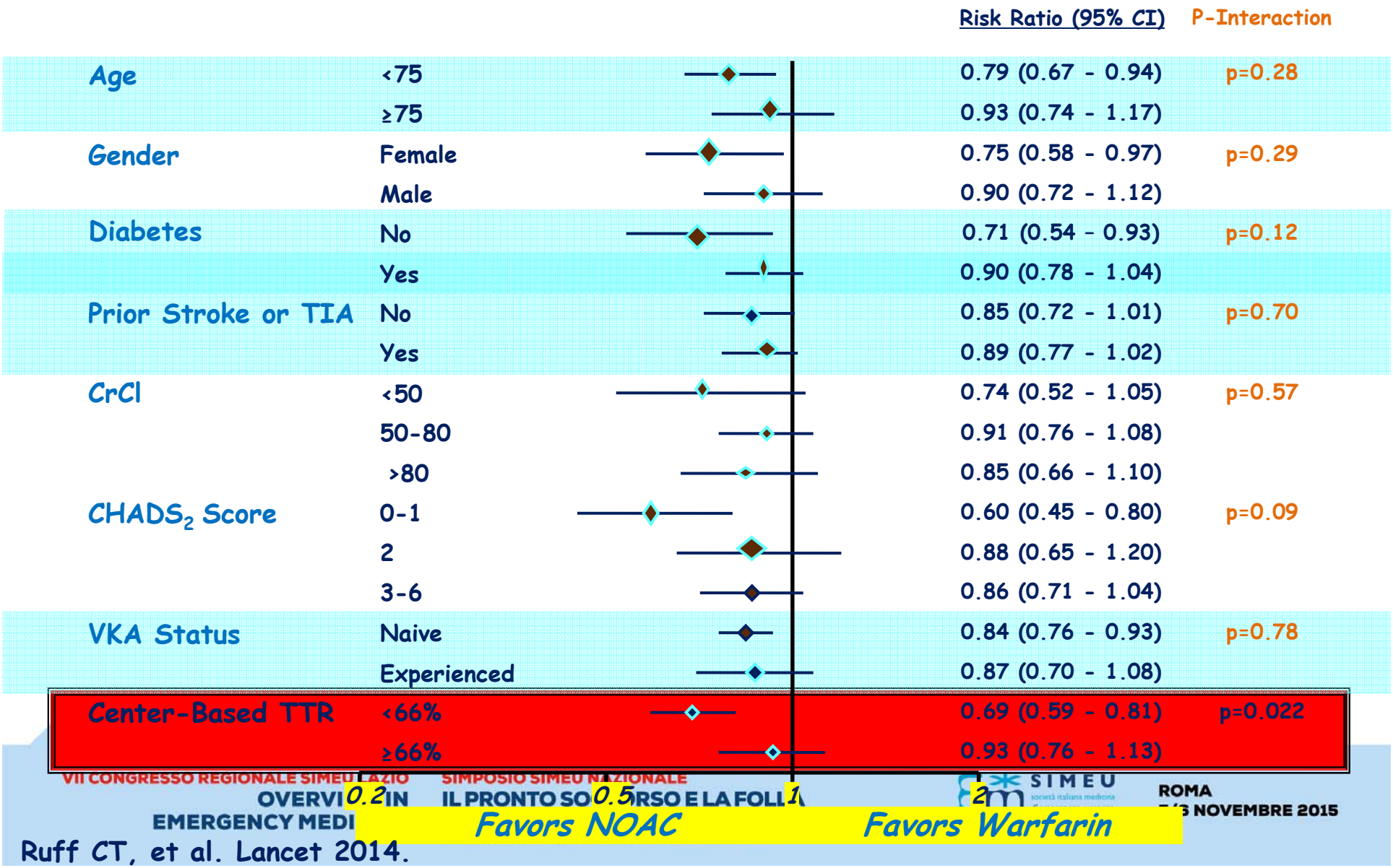
# All NOACs: Major Bleedings

## 'Low dose' regimens for dabigatran and edoxaban




Ruff CT, et al. Lancet 2014

# Subgroups: Major Bleeding




Ruff CT, et al. Lancet 2014.

# I NAO sono tutti uguali? Parametri da considerare

- Efficacia nella riduzione dell'ictus
- Sicurezza
  - Sanguinamenti Maggiori
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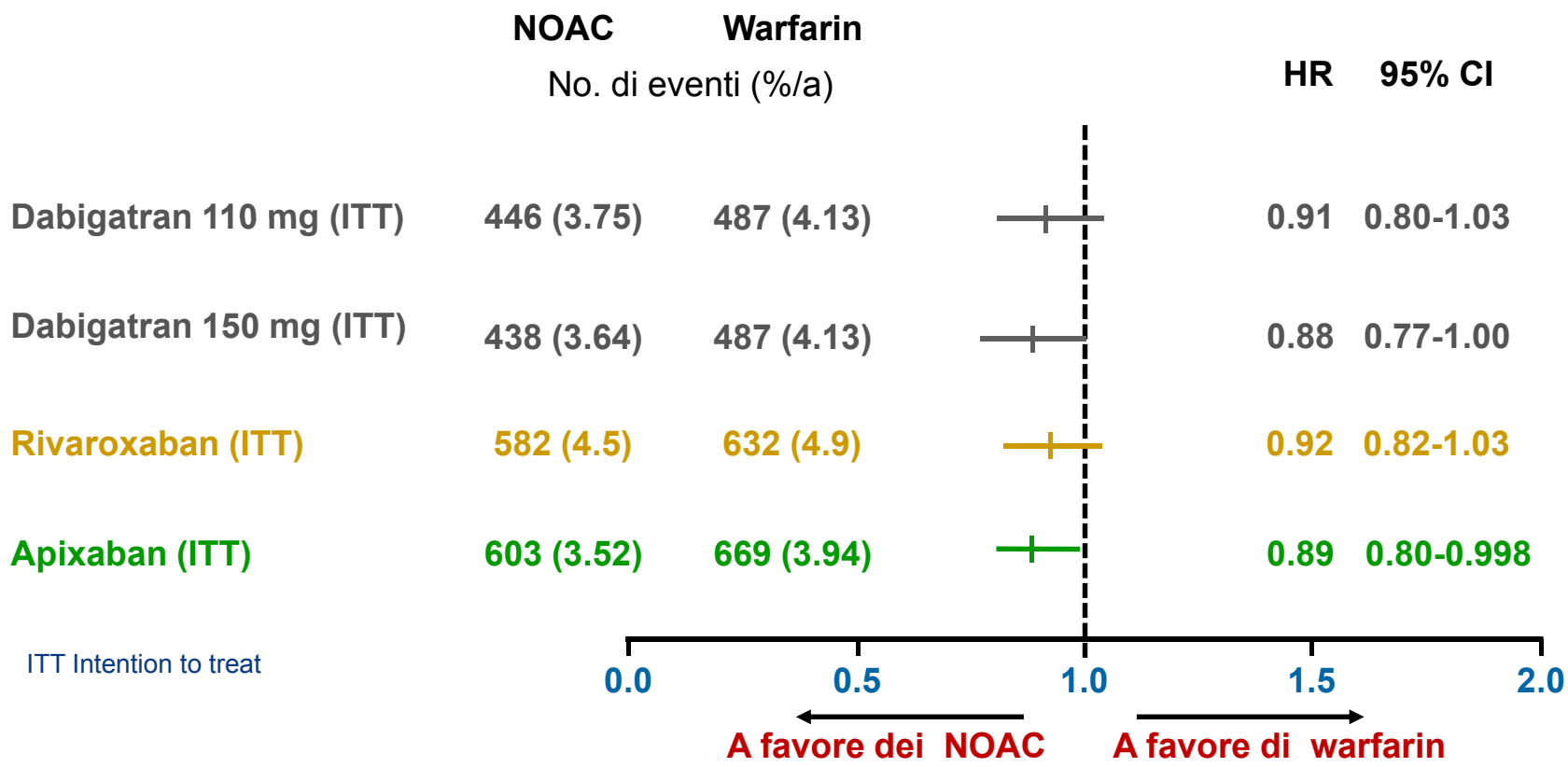
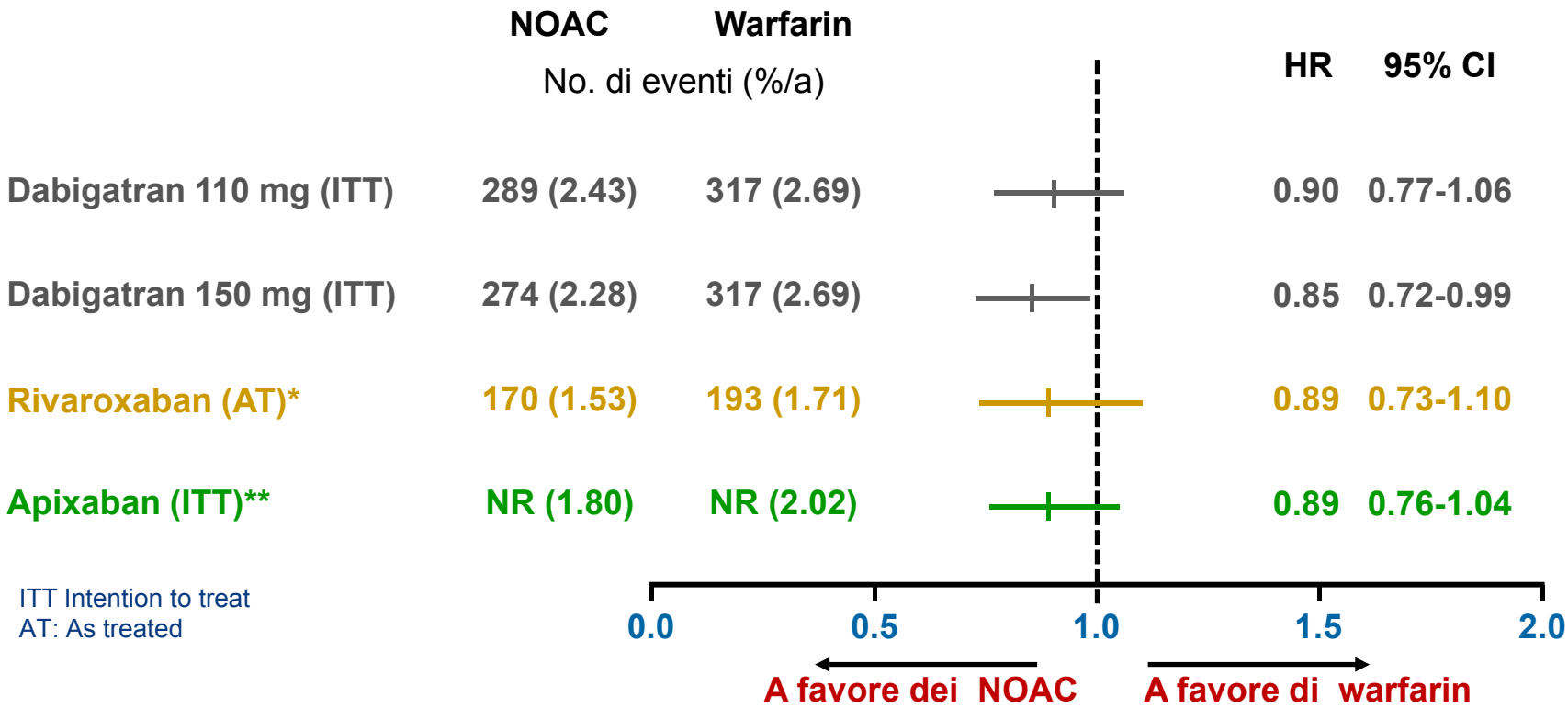
- **Mortalità**
- Maneggevolezza
  - Aderenza e persistenza
  - Facilità nella gestione del paziente
- Ma anche…
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - Cosa ci dicono i primi dati di Real Life dei NAO?

# NOAC *vs.* warfarin: mortalità da tutte le cause




Connolly et al. NEJM 2010;363:1875-6, suppl app. 2. Patel et al. NEJM 2011;365:883-91,suppl app. 3. Granger et al. NEJM 2011;365:981-92.

# NOAC *vs.* warfarin: mortalità CV




ITT Intention to treat
AT: As treated

***Dati ITT non disponibili***

****NR: numeri non riportati***

. Connolly et al. NEJM 2010;363:1875-6, suppl app. 2. Patel et al. NEJM 2011;365:883-91,suppl app. 3. Granger et al. NEJM 2011;365:981-92.

# Ridotta mortalità dopo un sanguinamento maggiore

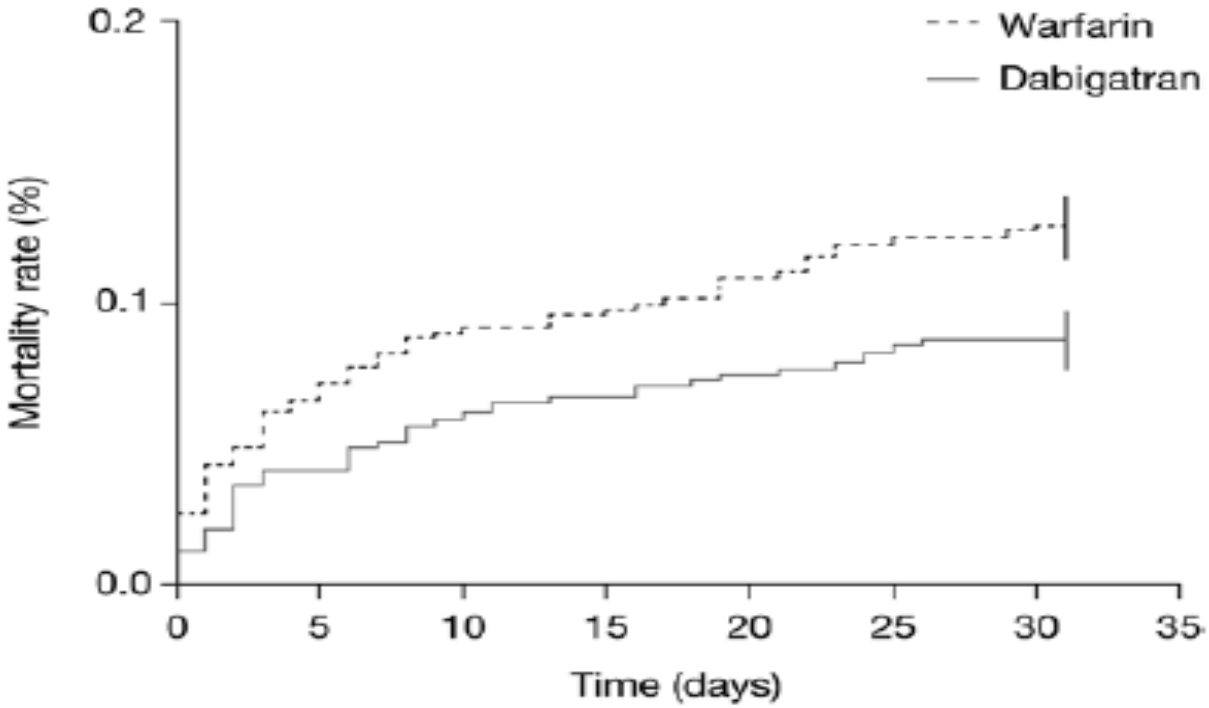



**Figure.** Thirty-day mortality rate after a major bleeding event.

Ammar Majeed et al Circulation 2013

# Ridotta mortalità dopo un sanguinamento maggiore

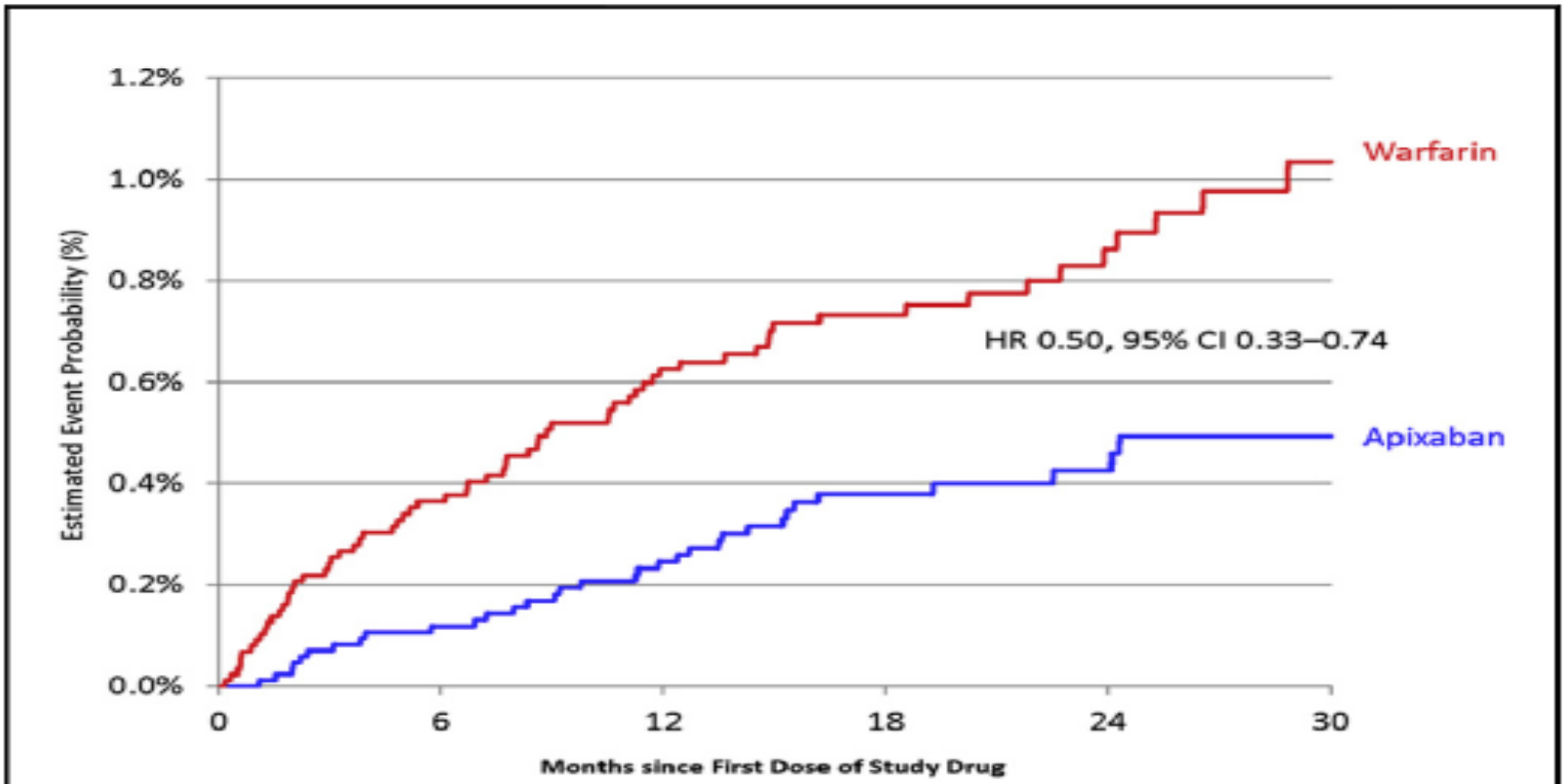



**Figure 1** **Major Bleeding Following by Death Within 30 Days**

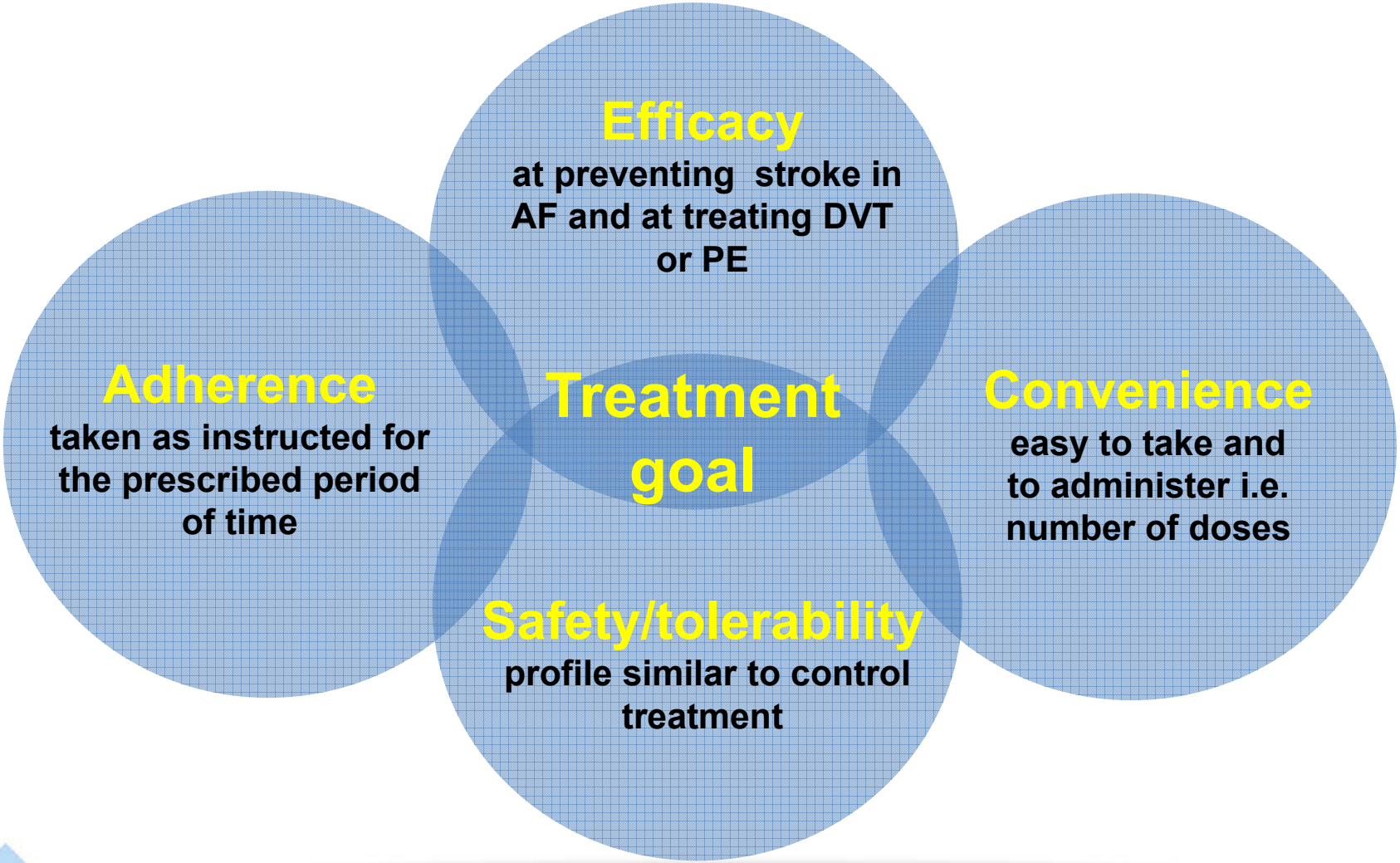
CI = confidence interval; HR = hazard ratio.

Hylek et al. *JACC* 2014

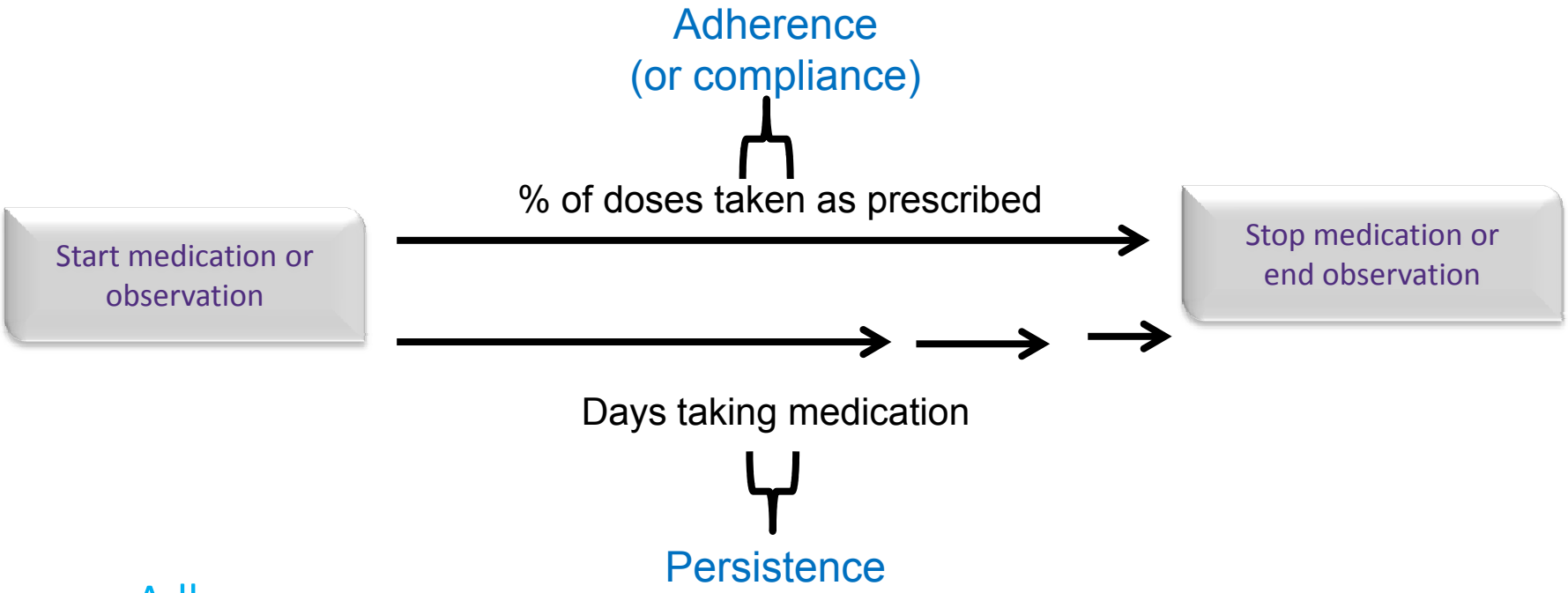
# I NAO sono tutti uguali? Parametri da considerare

- Efficacia nella riduzione dell'ictus
- Sicurezza
  - Sanguinamenti Maggiori
  - Sanguinamenti Gastrointestinali
- Mortalità
- **Maneggevolezza**
  - **Aderenza e persistenza**
  - **Facilità nella gestione del paziente**
- Ma anche…
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - Cosa ci dicono i primi dati di Real Life dei NAO?

# *An effective antithrombotic treatment could combine in any single patient …..*



# A shared understanding of the different terms




- Adherence
  - The extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen
  - Percentage of doses taken as prescribed
- Persistence
  - Duration of time from initiation to discontinuation of therapy
  - Days taking medication (without exceeding permissible gap)

Cramer *et al*, *Value Health* 2008;11:44–47

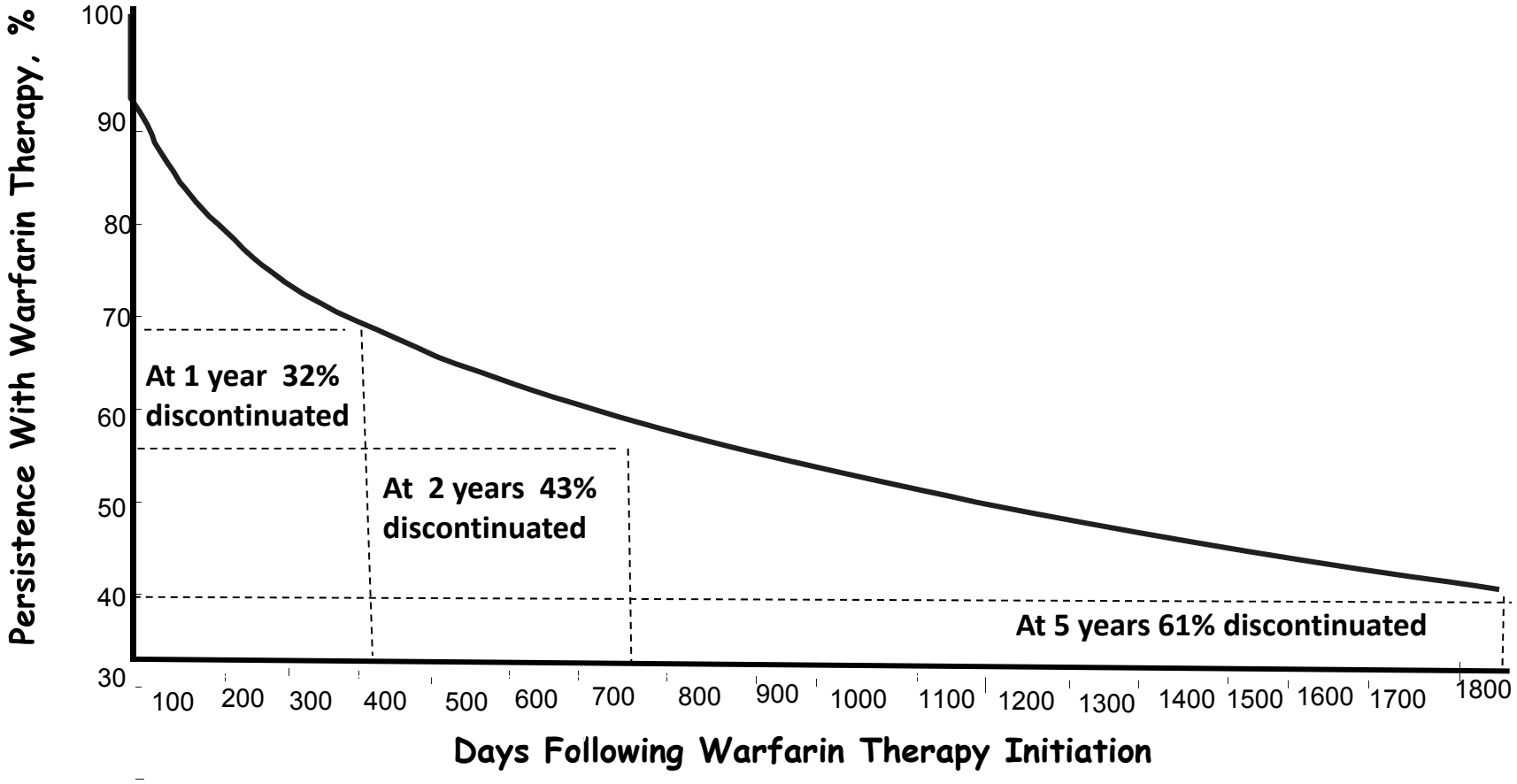
AIFA
Agenzia Italiana del Farmaco

**Per aderenza alla terapia si intende il conformarsi del paziente alle raccomandazioni del medico riguardo ai tempi, alle dosi e alla frequenza nell'assunzione del farmaco per l'intero ciclo di terapia.**

La scarsa aderenza alle prescrizioni del medico è la principale causa di non efficacia delle terapie farmacologiche ed è associata a un aumento degli interventi di assistenza sanitaria, della morbilità e della m
si
M
minori complicanze associate alla malattia, maggiore sicurezza ed efficacia dei trattamenti e riduzione dei costi per le terapie.
C'è un paradigma clinico, spesso affermato, secondo cui più farmaci vengono prescritti a un paziente, maggiore è la probabilità di non conformità. Ciò è vero soprattutto in un anziano con capacità visive o funzione cognitiva ridotte

**L'aderenza alle terapie è pertanto fondamentale per la sostenibilità del SSN.**

# Real-life Persistence to VKA is Suboptimal



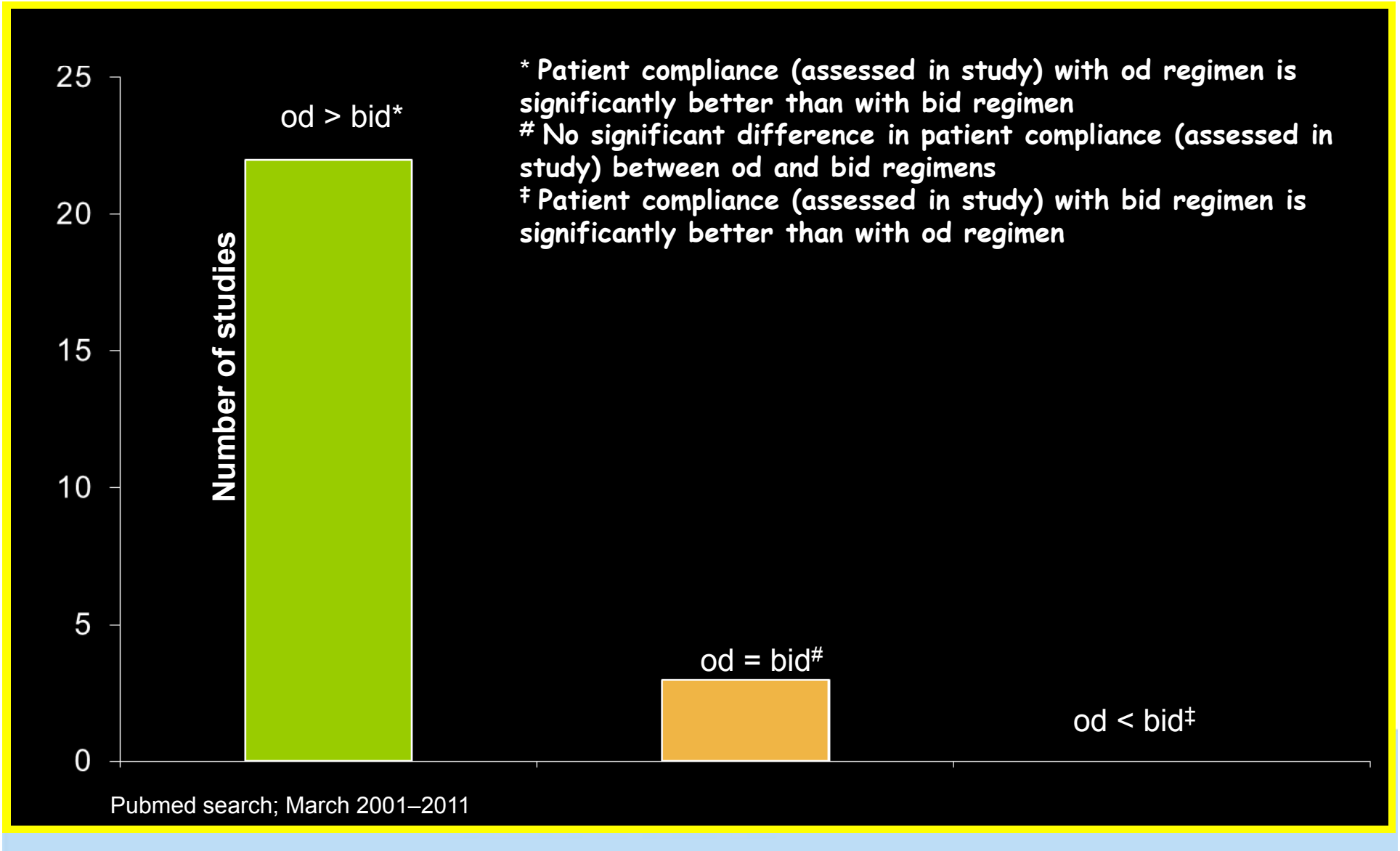

N=125.195 new VKA users with AF



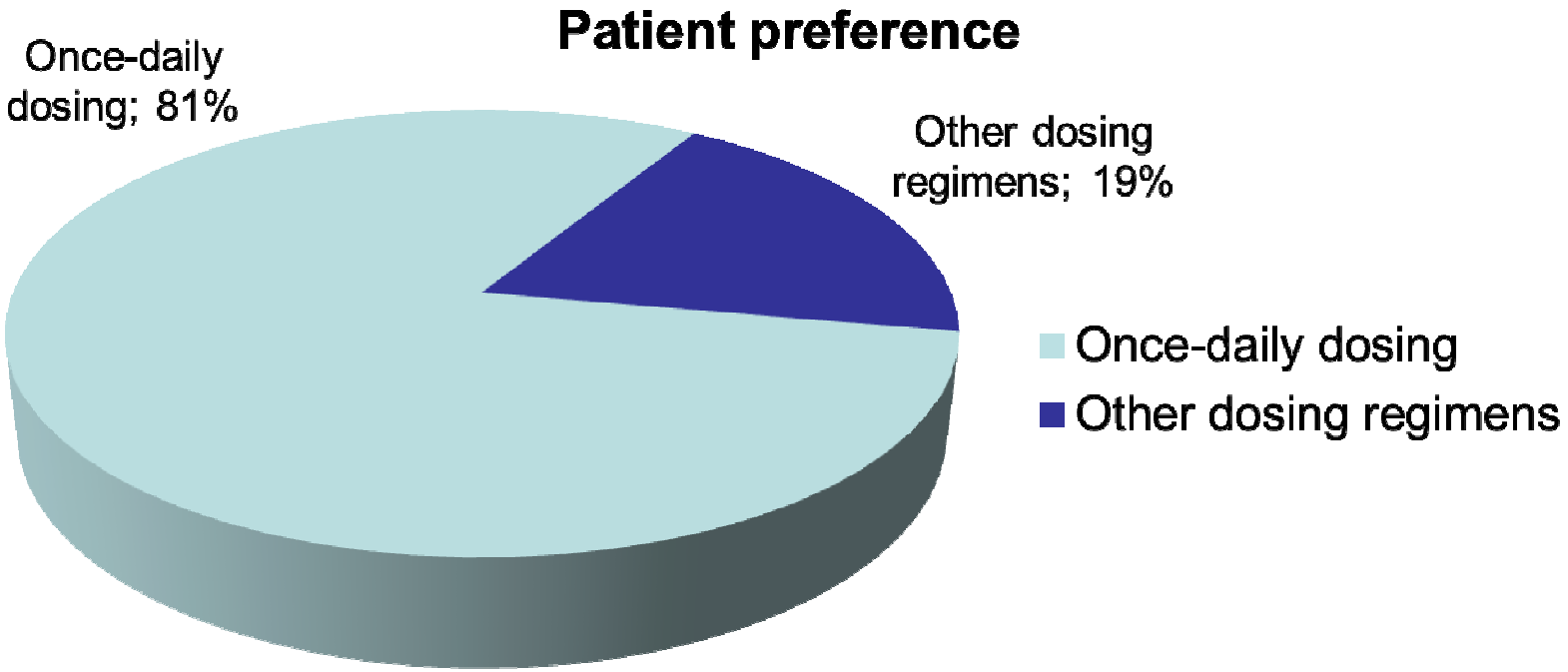
*Gomes et al. Arch Intern Med 2012;172:1687-9*

# Compliance with od versus bid regimens is generally better for chronic conditions

**Number of studies that directly assessed compliance**



# Patients with prefer OD dosing in oral anticoagulation

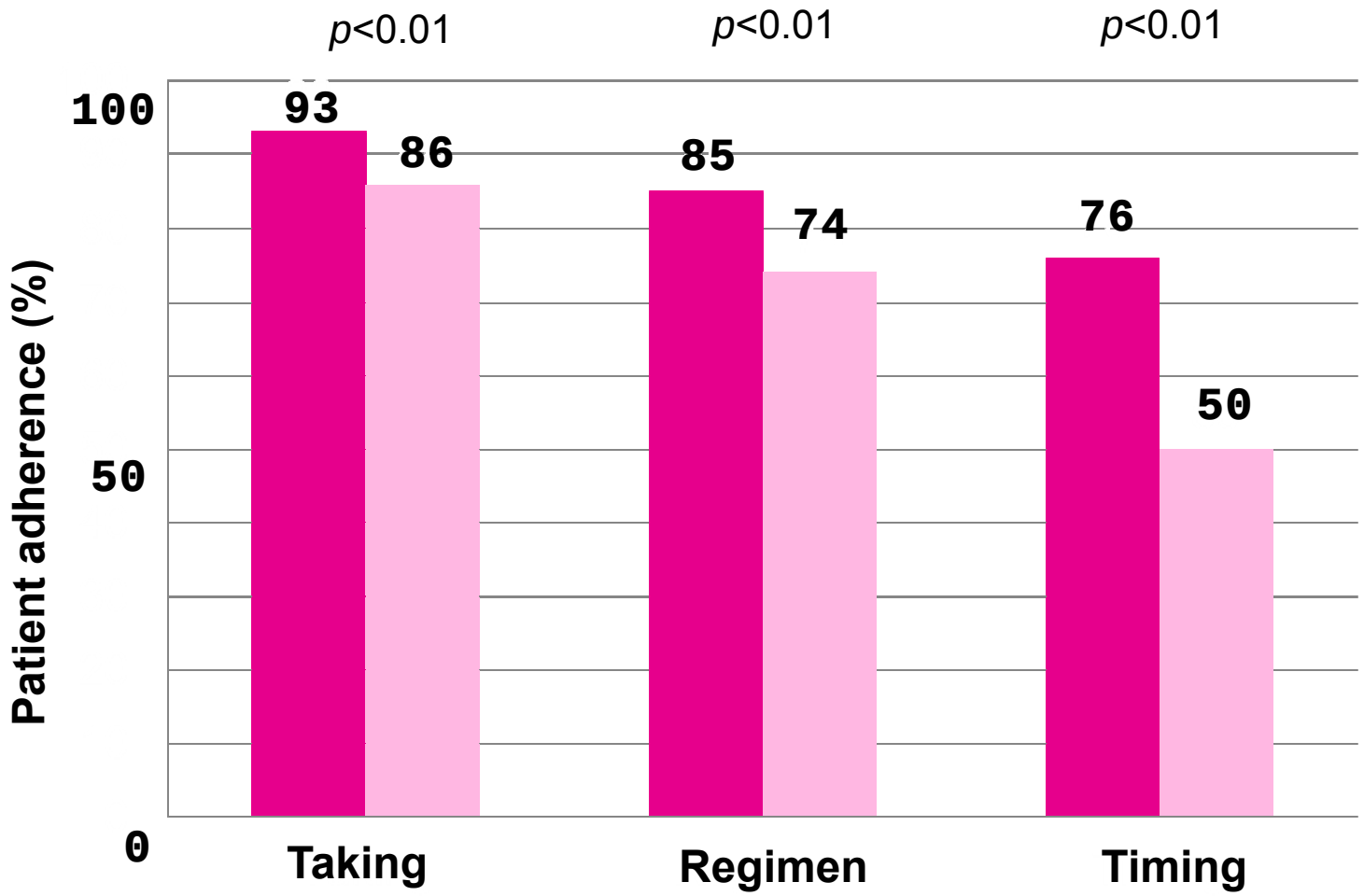



AF patients felt once daily dosing made it easier to follow their physician's instructions and was consistent with their habit of taking medication once daily

Data based on findings from the EUPS-AF study which conducted structured telephone interviews with AF patients >18 years or individuals who were receiving anticoagulation for a heart rhythm disturbance, between February and July 2011. A total of 1,507 patients took part in the survey.

Zamorano *et al*, as presented at ESC 2012

# *CV medication adherence:*
# *od* is associated with higher adherence than bid




OD

BID

Adherence calculated by three measures, in order of increasing strictness:

- **Taking** – Number of bottle cap openings divided by the prescribed number of doses.
- **Regimen** – Percentage of days with the appropriate number of doses taken.
- **Timing** – Percentage of near optimal inter-administration intervals.

Coleman CI. Curr Med Res Opin. 2012;28(5):1–12

# European Heart Rhythm Association Practical Guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation

## Practical considerations

(1) A once daily (qd) dosing regimen was related to greater adherence vs. bid regimen in cardiovascular patients,[39] and in AF patients (for diabetes and hypertension drugs).[40] It is likely that also for NOACs a qd dosing regime is best from a compliance perspective, but it is unknown whether any regimen is superior in guaranteeing the clinical thromboembolic preventive effects and the safety profile as seen in the clinical trials.

(2) Patient education on the importance of strict adherence is of utmost importance. Many simultaneous approaches should be employed in this regard: leaflets and instructions at initiation of therapy; a patient anticoagulation card; group sessions; re-education at every prescription renewal. There is room and potentially a need to develop new tools to enhance compliance with NOACs.

(3) Family members should be involved in this education, so that they too understand the importance of adherence, and help the patient in this regard.

EHRA Practical Guide, Europace, 2013

# Farmacodinamica regime od

- **Rivaroxaban**
  - inibisce:
    - attività FXa libero = $IC_{50}$ 0,7 nM
    - attività protrombinasi = $IC_{50}$ 2,1 nM

- $C_{trough}$ (conc. dopo 24 ore) con 20 mg ≈3,5-5,5 nM

**La concentrazione minima nelle 24 ore è sempre sufficiente a inibire adeguatamente il FXa**

# Compliance al Rivaroxaban Dresden Registry

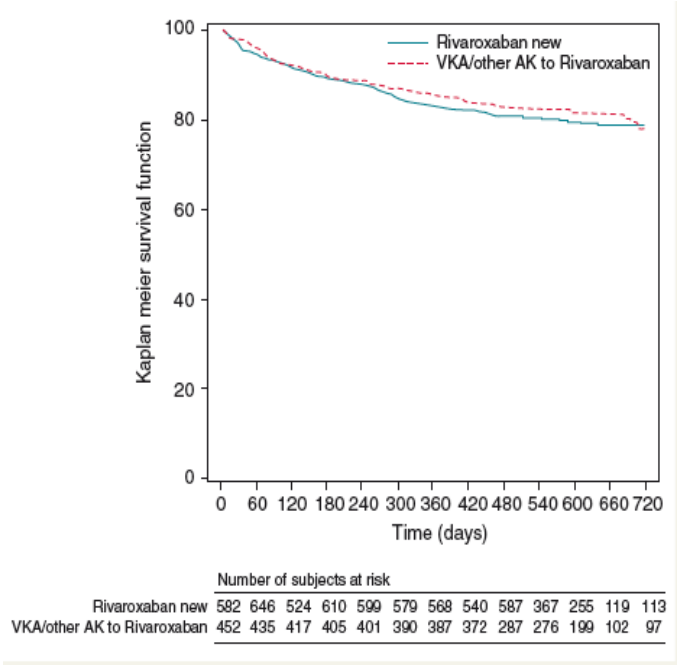



**Table 4** Cox proportional hazard model of potential risk factors for rivaroxaban discontinuation

| Baseline variable | HR (95% CI) | No discontinuation vs. discontinuation (%) | *P*-value |
|---|---|---|---|
| VKA pretreatment (yes vs. no) | 0.85 (0.65–1.12) | No: 18.9%<br>Yes: 18.0% | 0.25 |
| BMI (normal vs. underweight) | 0.74 (0.55–0.99) | Normal: 21.8%<br>Underweight: 20.0% | 0.04 |
| Heart failure (yes vs. no) | 1.41 (1.08–1.85) | No: 16.1%<br>Yes: 22.5% | 0.01 |
| Arterial hypertension (yes vs. no) | 0.73 (0.52–1.01) | No: 22.4%<br>Yes: 17.7% | 0.06 |
| Diabetes (yes vs. no) | 1.35 (1.03–1.77) | No: 16.4%<br>Yes: 21.7% | 0.03 |
| Prior TIA, stroke or systemic embolism (yes vs. no) | 1.34 (0.95–1.87) | No: 17.7%<br>Yes: 23.3% | 0.09 |
| Renal dysfunction (yes vs. no) | 1.32 (0.92–1.90) | No: 17.7%<br>Yes: 24.5% | 0.13 |

BMI, body mass index; CI, confidence interval; TIA, transient ischaemic attack; VKA, vitamin K antagonist

**Persistence with rivaroxaban therapy is high, with a discontinuation rate of ~15% in the first year of treatment and few additional discontinuations thereafter.**

Beyer-Westendorf J. et al. Europace 2015

# Facilità gestione paziente

1. Nessun effetto su aggregazione piastrinica ed emostasi primaria
2. Minima variabilità di risposta inter- e intra-soggetto
3. Biodisponibilità prevedibile
4. Basso potenziale di interazione con alimenti e farmaci

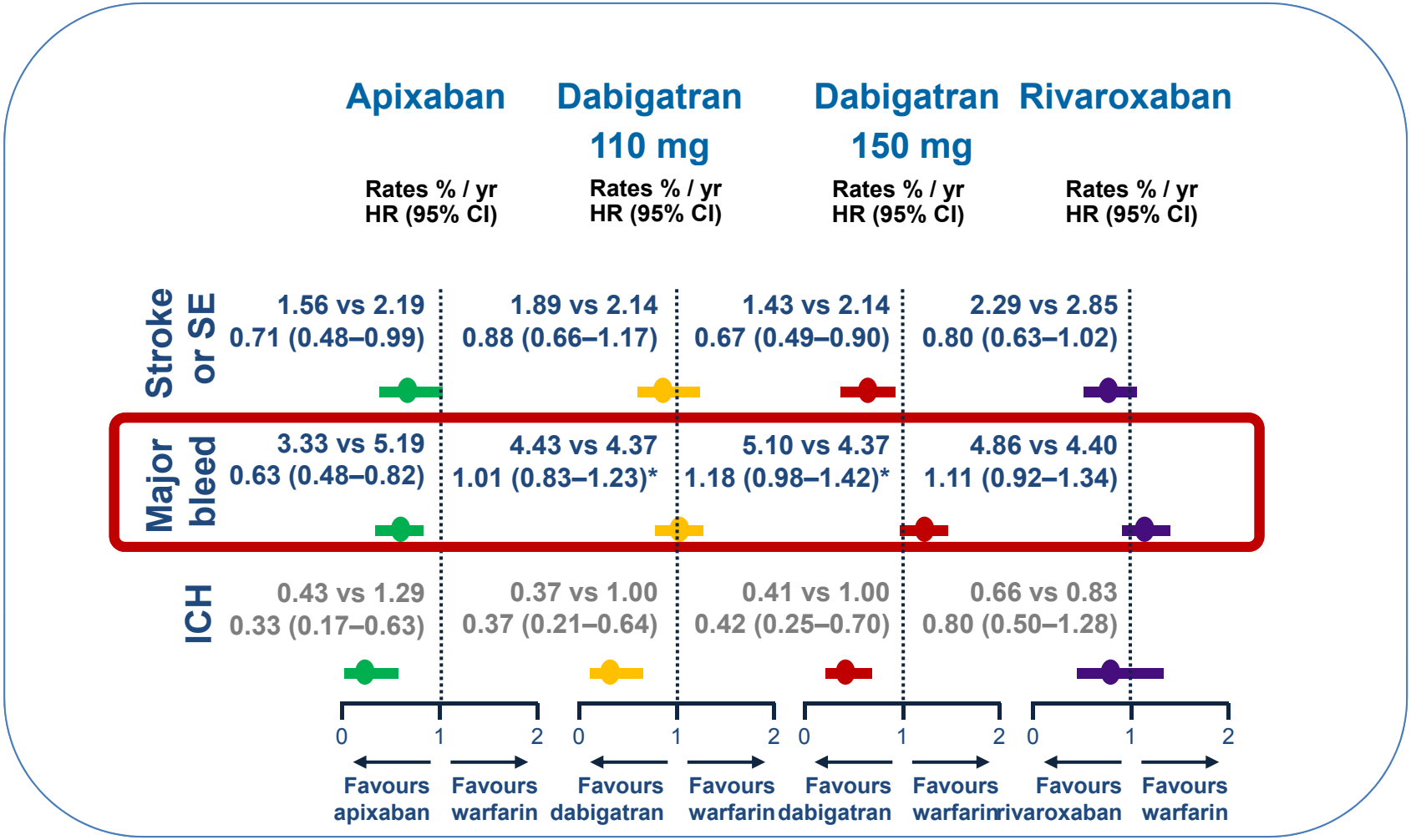
***Nel complesso il loro effetto anticoagulante è stabile e prevedibile. Pertanto, non sono richiesti controlli dell'assetto coagulativo durante la terapia per verificare l'effetto o definire la dose ottimale.***

*2012 focused update of the ESC Guidelines for the management of AF*

# I NAO sono tutti uguali? Parametri da considerare

- Efficacia nella riduzione dell'ictus
- Sicurezza
  - Sanguinamenti Maggiori
  - Sanguinamenti Gastrointestinali
- Mortalità
- Maneggevolezza
  - Aderenza e persistenza
  - Facilità nella gestione del paziente
- **Ma anche…**
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - Cosa ci dicono i primi dati di Real Life dei NAO?

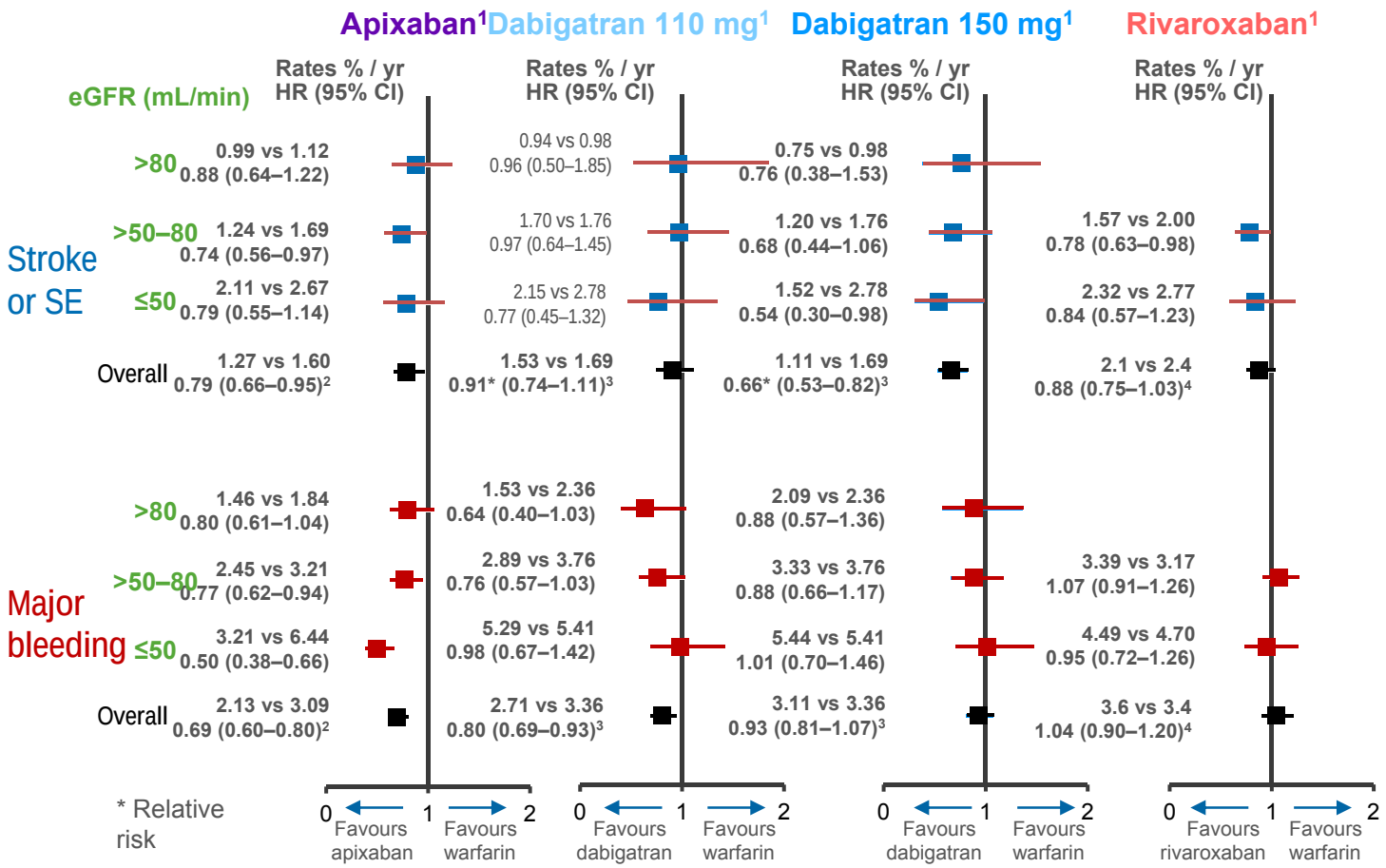
# Efficacia e sicurezza dei NAO in pazienti anziani >75




p<0.001 vs warfarin; HR, hazard ratio; CI, confidence interval; ICH, intracranial haemorrhage; SE, systemic embolism.

Capranzano P et al. *Expert Rev Cardiovasc Ther* 2013;11:959-73;

# Efficacia e sicurezza dei NAO in base ai livelli di funzione renale





1. *Capranzano P et al. Expert Rev Cardiovasc Ther 2013;11:959-73;* 2. Granger *et al. N Engl J Med* 2011;365:981-92; 3. Connolly *et al. N Engl J Med* 2009;361:1139-51; 4. Patel *et al. N Engl J Med* 2011;365:883-91

# Perché è necessario considerare la ClCr al momento dell'arruolamento del paziente?

291 (32,4%) perdita eGFR ≥5 ml/min/anno

| Classi eGFR | Rapido declino eGFR |
|---|---|
| >90 ml/min/1.73 $m^2$ | 97 (33,3%) |
| 89-60 ml/min/1.73 $m^2$ | 148 (50,9%) |
| 59-30 ml/min/1.73 $m^2$ | 44 (15,1%) |
| <30 ml/min/1.73 $m^2$ | 2 (0,7%) |

2015 Violi BMJ Open

*Capranzano et al. Expert Rev. Cardiovasc. Ther.* 11(8), 959-973 (2013)

# Pazienti con precedente Stroke: sicurezza dei NOACs

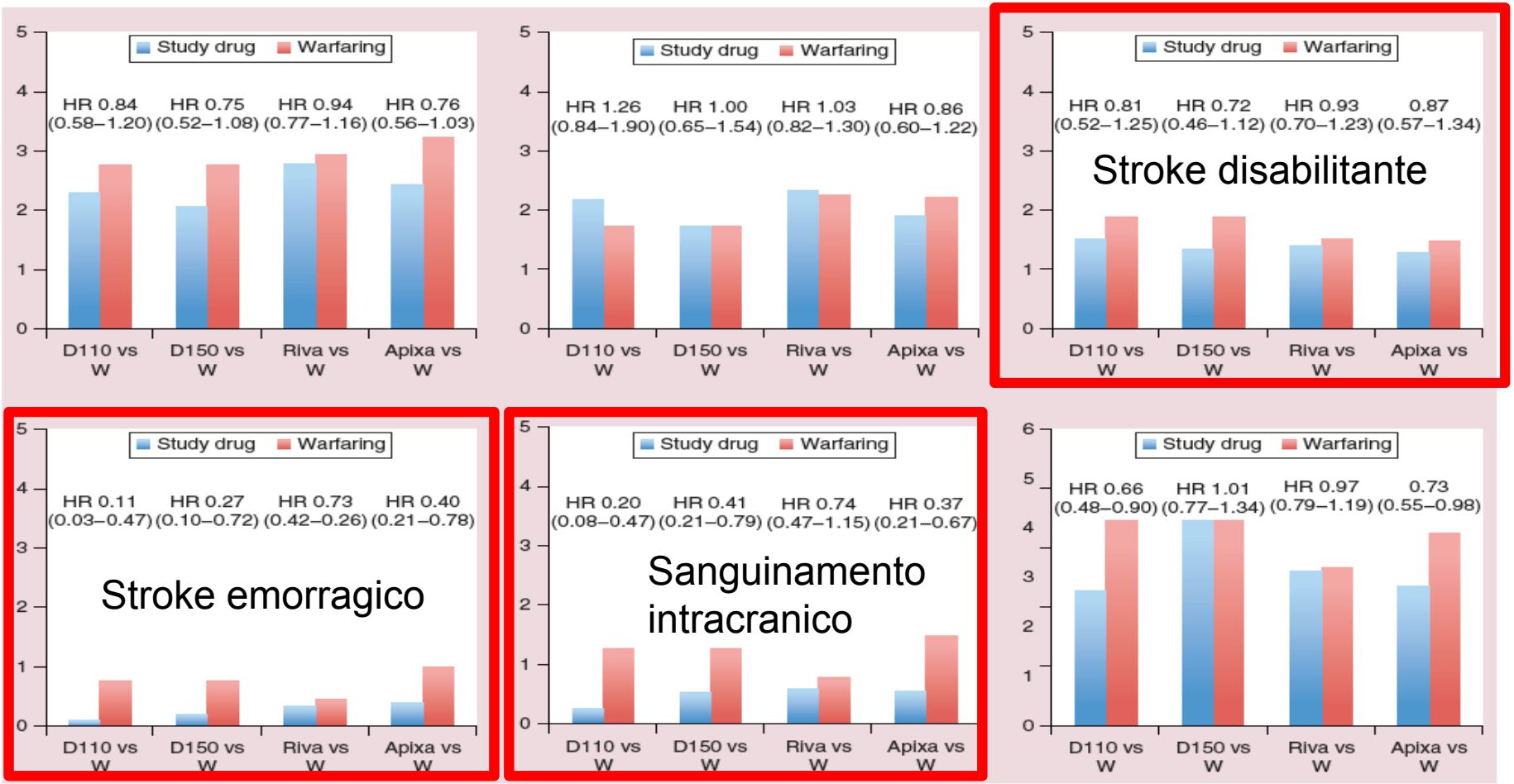



**Figure 4. Yearly rates and risk estimates of different outcomes with novel anticoagulants vs warfarin within patients with prior stroke or transient ischemic attack. (A)** Primary end point. **(B)** Ischemic or unknown stroke. **(C)** Fatal or disabling stroke. **(D)** Hemorrhagic stroke. **(E)** Intracranial bleeding. **(F)** Major bleeding.
The brackets include 95% confidence intervals.
D110: Dabigatran 110-mg; D150: Dabigatran 150-mg; HR: Hazard ratio; SE: Systemic embolism; W: Warfarin.

# I NAO sono tutti uguali? Parametri da considerare

- Efficacia nella riduzione dell'ictus
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  - Sanguinamenti Gastrointestinali
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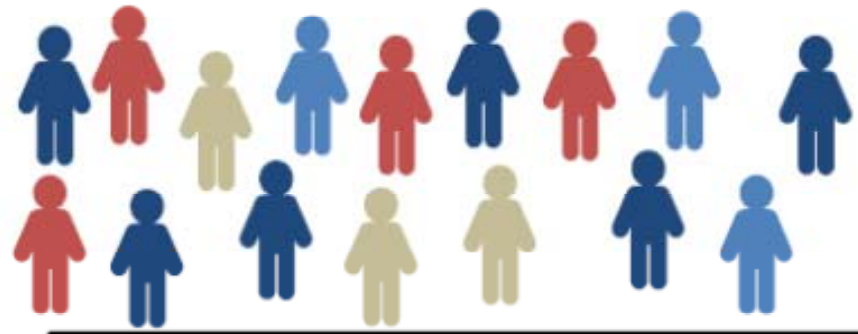
- **Ma anche…**
  - Popolazioni speciali (paziente anziano, con danno renale…)
  - **Cosa ci dicono i primi dati di Real Life dei NAO?**

# Testing and investigation of treatments should not end when a drug comes onto the market



**RCTs: tightly controlled patient population**

RCTs are gold-standard for evidence-based medicine but RWE is important to confirm safety and effectiveness in everyday practice

**Differing:**

- Age
- Race
- Co-morbidities
- Co-medications
- Adherence

RWE clarifies whether the results observed under the tightly controlled conditions of an RCT are also observed in everyday clinical practice

# "Real-life" data vs clinical trial data

| | "Real-life" | Clinical trial |
|---|---|---|
| **Enrols** | Unselected patients | Selected patients |
| **Primarily investigates** | Effectiveness<br>Safety<br>Management issues | Efficacy<br>Safety |
| **Sample size** | Determined by many variables, e.g. centre size, funding available for registry | Determined by required statistical power |
| **Key benefits** | Patients closely represent population that will receive intervention in everyday practice | Controlled environment; patients selected and carefully monitored |
| **Key limitations** | Procedures and event definitions may vary between centres and individuals; differences may not be identifiable; potential reporting bias e.g. 'Weber effect'; patient demographics/co-morbidities may influence clinical outcomes | Will results translate into everyday practice? |

# What robust comparative real-world data are available for the NOACs?

| | Dabigatran | Rivaroxaban | Apixaban | Edoxaban |
|---|---|---|---|---|
| Total number of patients involved | > 250 000[1–7] | ~10 000[7] | Not available | Not available |
| Treatment-naïve NOAC patients vs warfarin* | >118 000[1–5,7] | >5000[7] | – | – |
| Effectiveness vs warfarin? | ✓[1-4, 6] | – | – | – |
| Safety vs warfarin? | ✓[1-7] | ✓[7] | – | – |

**Clinical profiles confirmed by numerous studies of robust real-world evidence[1-7]**

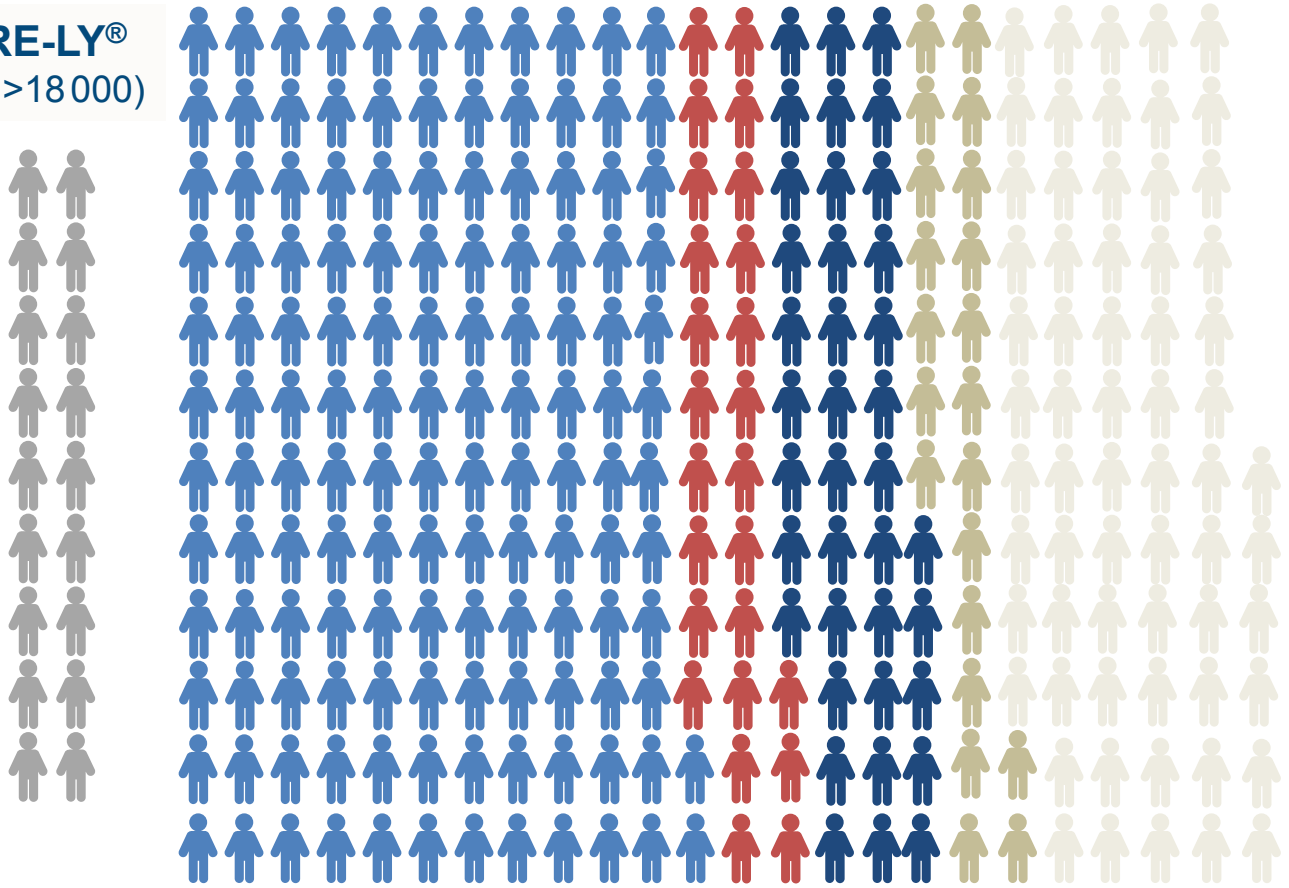
*For robust comparisons with warfarin which minimize confounding, only propensity-score matched or propensity-score-weighed data from OAC naive patients were included

1. Graham EJ et al. Circulation 2015;131:157–64; 2. Villines TC et al. Presented at AHA 2014; 3. Seeger JD et al. Presented at AHA 2014; 4. Lauffenburger JC et al. J Am Heart Assoc 2015;4:e001798; 5. Larsen TB et al. Am J Med 2014;127:650–6.e5
6. Larsen TB et al. Am J Med 2014b;127:329–36.e4; 7. Abraham NS et al. BMJ. 2015 Apr 24;350:h1857

# Growing body of real-world experience from >250 000 patients confirms safety and efficacy profile of DABIGATRAN

**Clinical practice** (N>250 000 patients)

**RE-LY®** (N>18 000)



- FDA Medicare study (N>134 000)[1]
- US Dept of Defense database (N>25 000)[2]
- 2 US insurance databases (N>38 000)[3]
- Danish observational studies (N>21 000)[4,5]
- US insurance database (N>64 000)[6]

**1.** Graham et al. Circulation 2015; **2.** Villines et al. Circulation 2014; **3.** Seeger et al. Circulation 2014; **4.** Larsen et al. Am J Med 2014a; **5.** Larsen et al. Am J Med 2014b; **6.** Lauffenburger et al. J Am Heart Assoc 2015

RE-AL WORLD EVIDENCE

Clinical practice data of dabigatran etexilate

# Cardiovascular, bleeding, and mortality risks in elderly Medicare patients t for non-valvular at

Graham DJ et al. Circulat

**MEDICARE**

**>134 000 OAC-naïve dabigatran or VKA users**

**>37500 patient years follow-up**

**aged≥65 aa**

American Heart Association.

edicare Patients Treated with
rial Fibrillation
nei Zhang, Mary Ross Southworth,
ing, Monika Houstoun, Thomas E.
Kelman

0, 2014;
nville Avenue, Dallas, TX 75231
l rights reserved.
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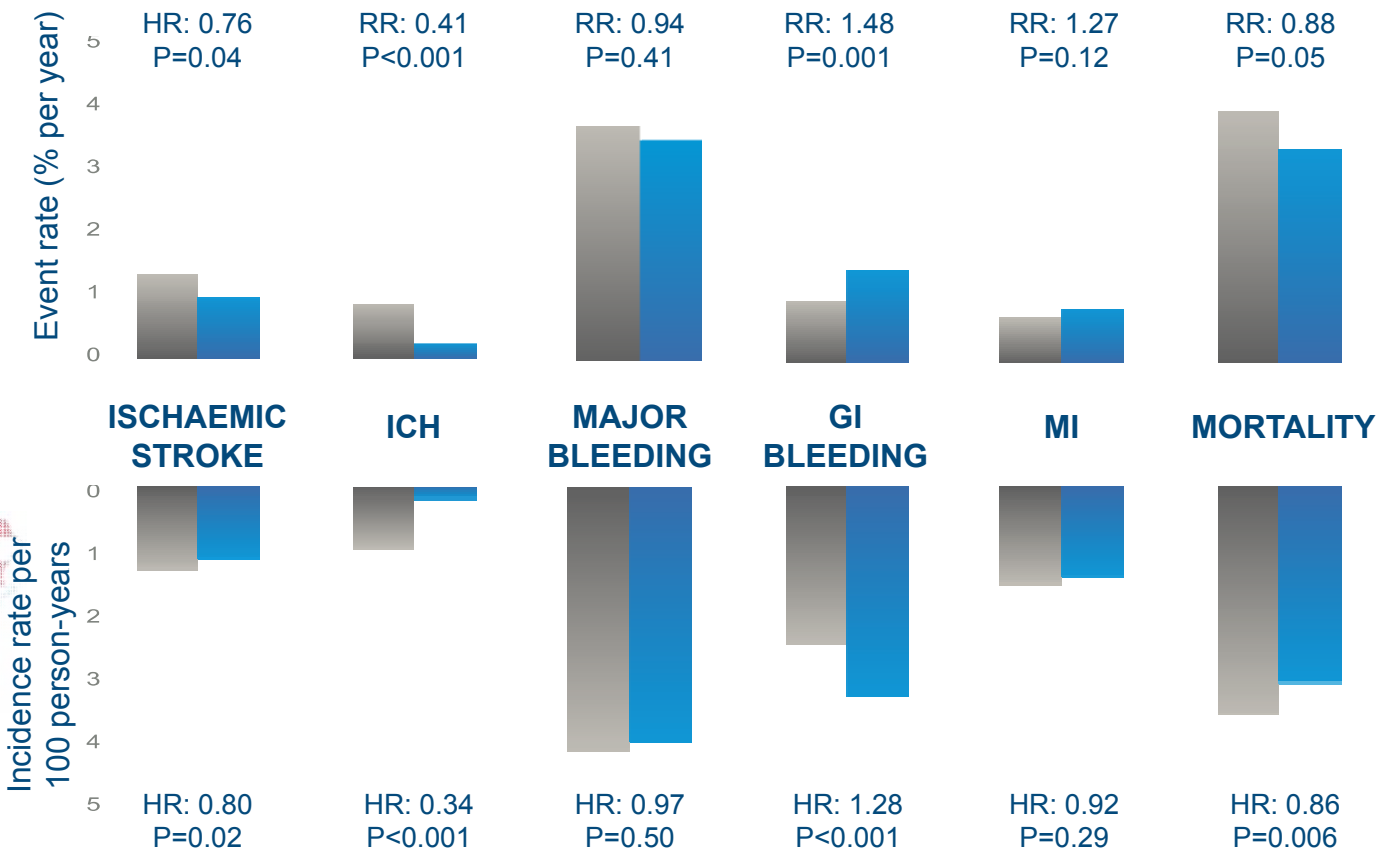
The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2014/10/30/CIRCULATIONAHA.114.012061

# Independent FDA study of Medicare patients **mirrors** the favourable benefit–risk profile of dabigatran from RE-LY®

## INDEPENDENT data

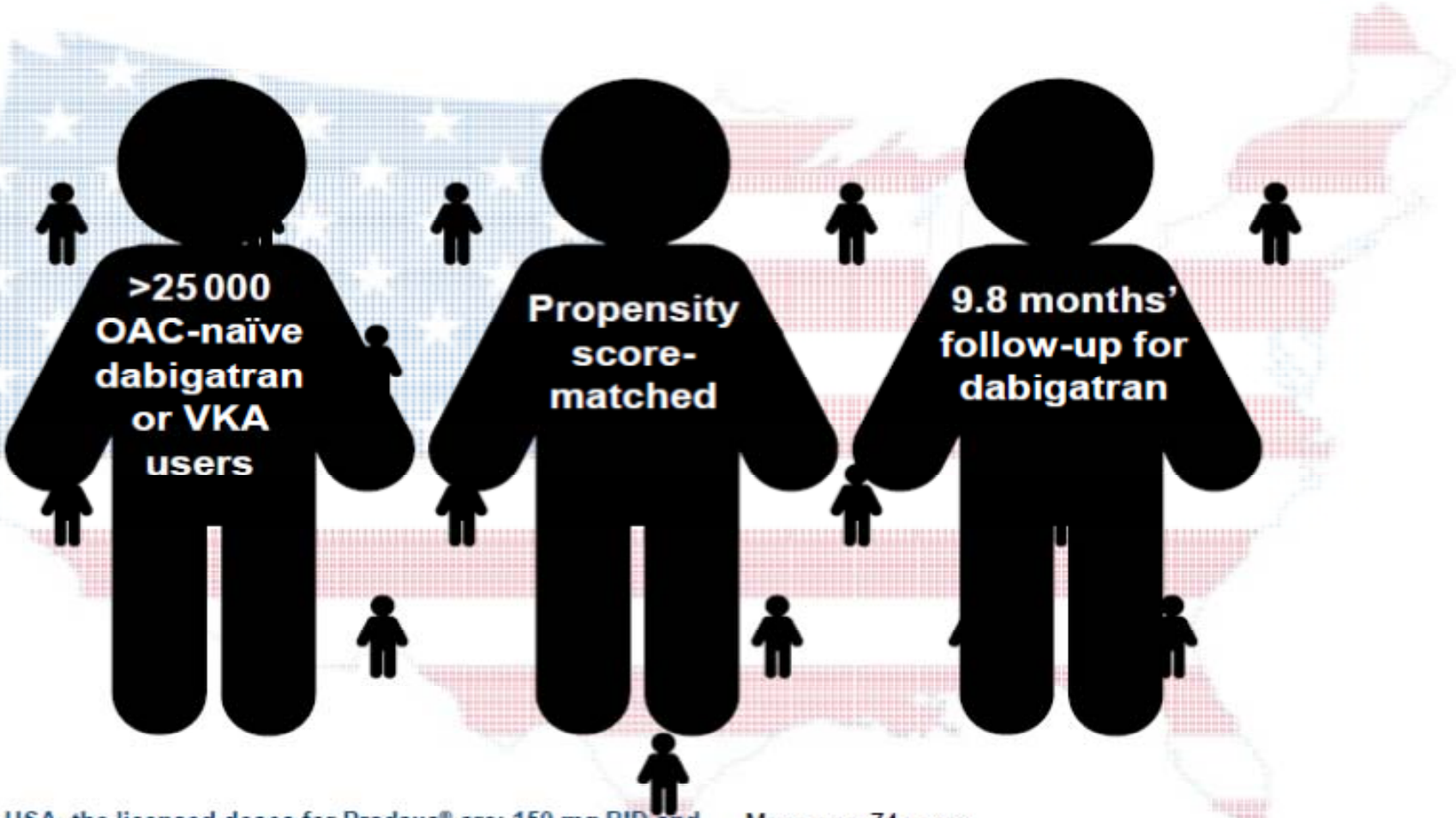





**In the EU, dabigatran 110 mg BID is indicated for certain patients, and was shown to be as effective vs VKA for prevention of stroke/SE. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study**

**1.** Graham et al. Circulation 2015; **2.** Connolly et al. N Engl J Med 2009; **3.** Connolly et al. N Engl J Med 2010; **4.**Connolly et al. N Engl J Med 2014

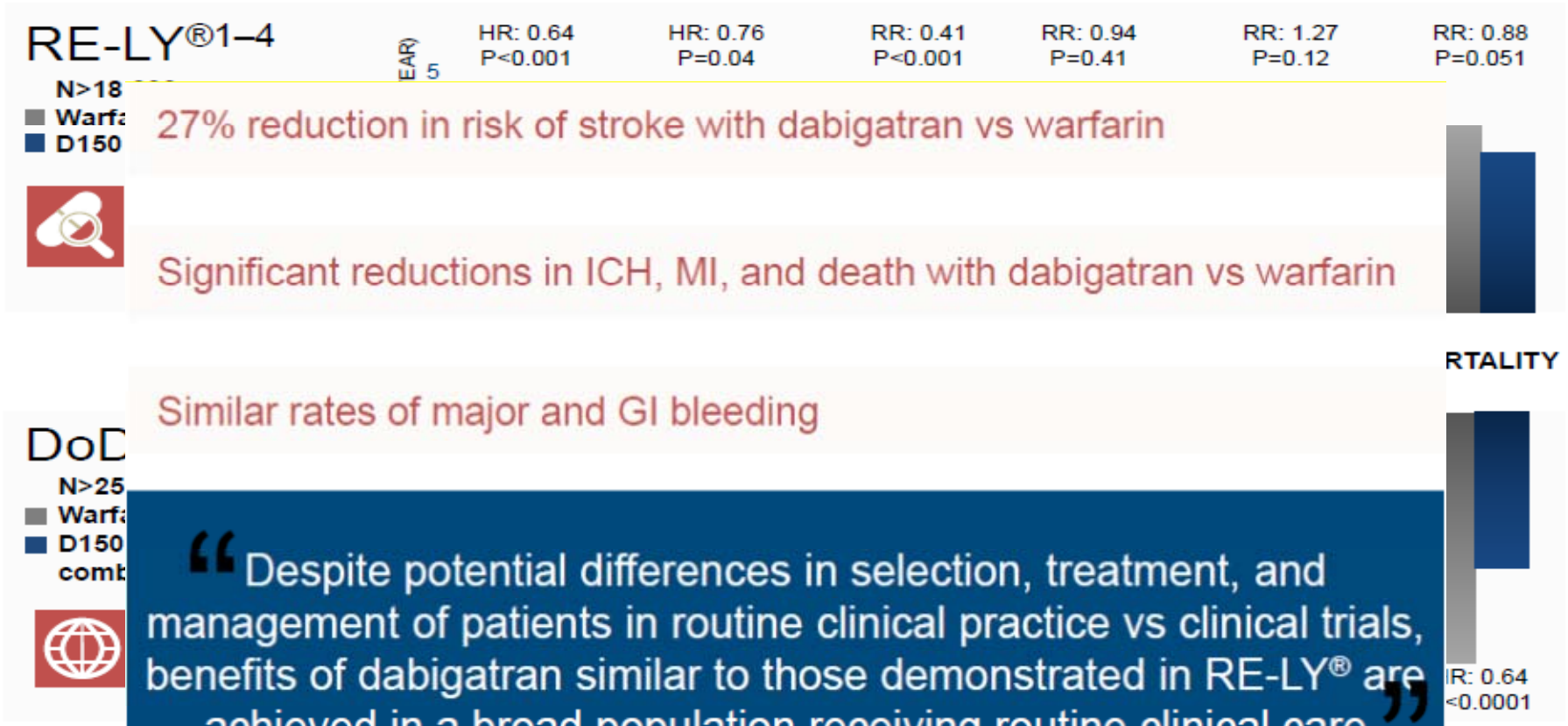
# US DoD study assessed safety and effectiveness of dabigatran vs warfarin in a large cohort of elderly patients




In the USA, the licensed doses for Pradaxa® are: 150 mg BID and 75 mg BID for the prevention of stroke and systemic embolism in adult patients with NVAF

Mean age: 74 years
OAC, oral anticoagulant; VKA, Vitamin K antagonist
Villines TC et al. Circulation 2014;130:A18353

# US DoD database showed clear consistency in outcomes with data from RE-LY®




"Despite potential differences in selection, treatment, and management of patients in routine clinical practice vs clinical trials, benefits of dabigatran similar to those demonstrated in RE-LY® are achieved in a broad population receiving routine clinical care"

**In … was shown to be as effective vs VKA for prevention of stroke/SE. RE-LY® was a PROBE (prospective, randomized, open-label with blinded endpoint evaluation) study**

1. Connolly SJ et al. N Engl J Med 2009; 361:1139–51
2. Connolly SJ et al. N Engl J Med 2010;363:1875–6

# NOAC-Register Dresden

- **Ampio Registro Prospettico Regionale relativo all'assistenza quotidiana di pz trattati con nOAC.**

- **Coordinatore Jan-Beyer Westendorf** (angiologo dell'Ospedale Carl Gustav Carus dell'Università Tecnica di Dresda)

- **Analizzati 2231 pazienti in un periodo compreso tra il 1°Ottobre 2011 e il 18 Giugno 2013.**

- **E' stata valutata la sicurezza dello switching anticoagulativo da VKA a Rivaroxaban (Dabigatran), sia per gli eventi cardiovascolari che emorragici.**

# Real-life efficacy and safety of rivaroxaban for stroke prevention in AF: results of the NOAC registry (NCT01588119)

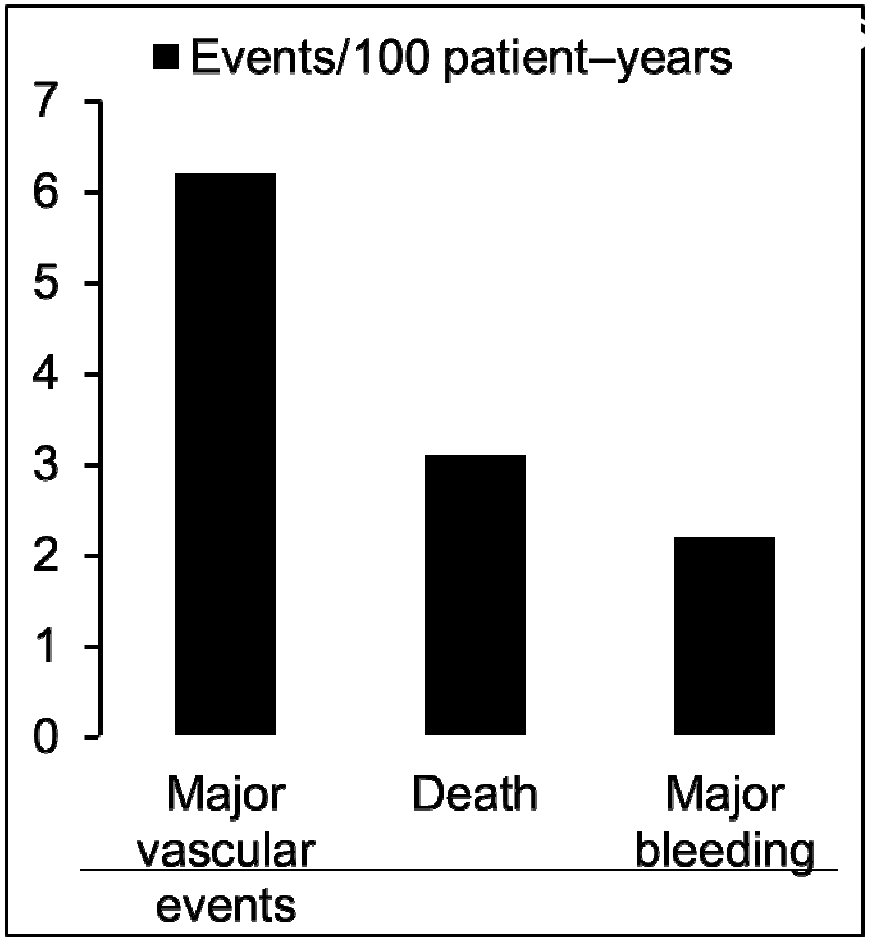
**Objective:** To evaluate the efficacy and safety of rivaroxaban in patients with AF in daily care and adherence to treatment

**Study design:** Prospective, non-interventional registry (network of >230 physicians)

- Patients receiving rivaroxaban (n=967) followed up prospectively by telephone
- All events adjudicated centrally using standard definitions

**Conclusion:** In unselected patients, rivaroxaban demonstrated:

- A good efficacy and safety profile
- Low rates of cardiovascular or major bleeding events
- High treatment adherence (90.7% at 9 months)




Any bleeding was observed at an incidence of 66.4 events per 100 patient–years

Beyer-Westendorf *et al*, 2013

# Rates, management and outcome of rivaroxaban bleeding in daily care: results from the Dresden NOAC registry

**Objective**

- To assess the rates of rivaroxaban-associated bleeding complications in daily care
- To assess the management of rivaroxaban-associated bleeding

**Design**

The Dresden NOAC multicentric registry in the administrative district of Dresden (Saxony), Germany, is a network of more than 230 physicians from private practices and hospitals

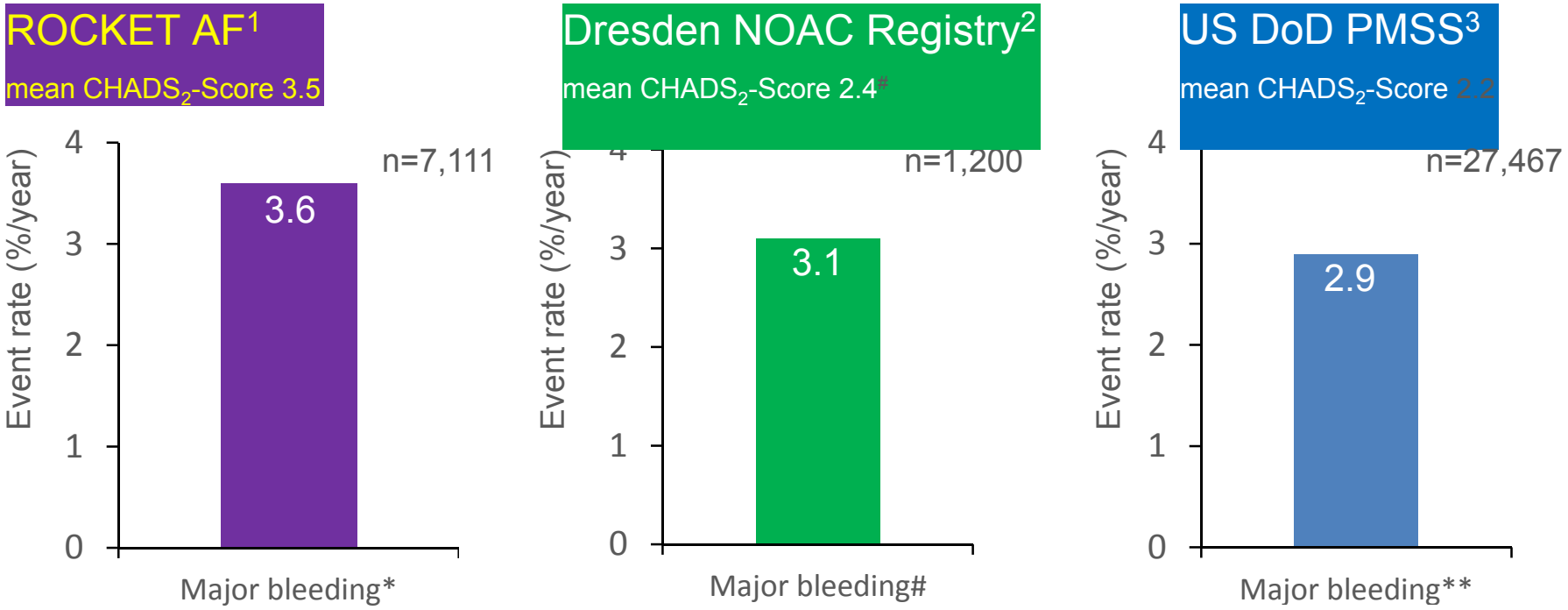
**Conclusions**

- Bleeding complications in rivaroxaban patients mainly consist of minor or NMCRB bleeding events that rarely require any treatment at all.
- Only approximately 6% of all bleeding events are MB events, which can be managed conservately by using tamponade, compression or RBC transfusions in approximately 60% of events.
- The remaining 40% of MB events required surgical or interventional treatment, but procoagulant therapy with PCC was rarely needed.



Beyer-Westendorf et al., *Blood* 2014

# Major Bleeding Rates with Rivaroxaban in Real Life Studies are Consistent with Findings from ROCKET AF




*Major bleeding definitions according to ISTH; # modified ISTH definition (additionally included surgical revision from bleeding)
**Major bleeding was defined by the Cunningham algorithm[3]
#55th ASH Meeting 2013, Oral presentation, Abstract 213, https://ash.confex.com/ash/2013/webprogram/Paper58333.html

1. Patel MR et al. *N Engl J Med* 2011; 365(10):883–891; 2. Beyer—Westendorf et al. Blood 2014;124(6); 955-962; 3. Tamayo S et al. Clin Cardiol. 2015;38(2):63–68

XANTUS

Post-marketing surveillance study

# Overvie
# Safety in AF patients

**Objective:** collect real-life data on AEs, bleeding, thromboembolic events and mortality in patients with non-valvular AF treated with rivaroxaban

**Population:**
Non-valvular AF (N=6000 in Europe), rivaroxaban treatment for stroke/non-CNS systemic embolism prevention

Rivaroxaban; dose and treatment duration at physician's discretion

Data collection at initial visit, hospital discharge (if applicable) and quarterly*

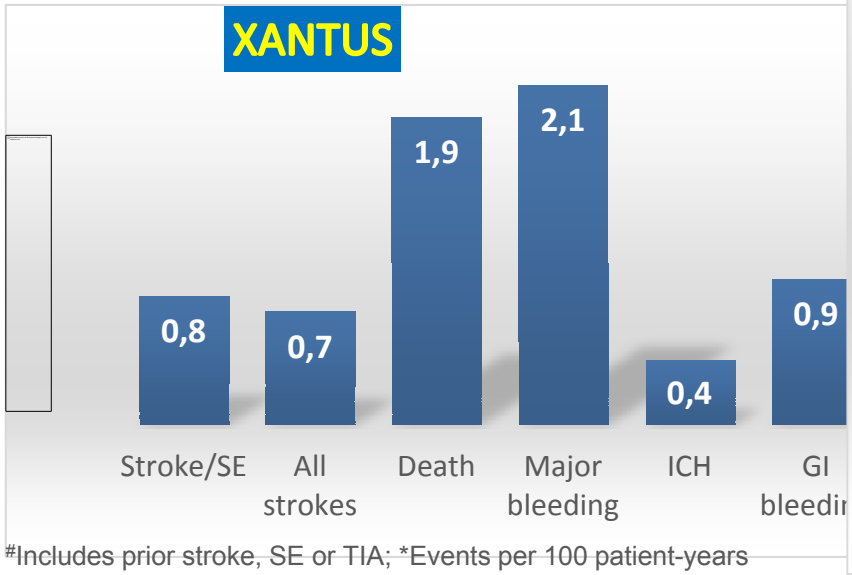
Final visit: 1 year#

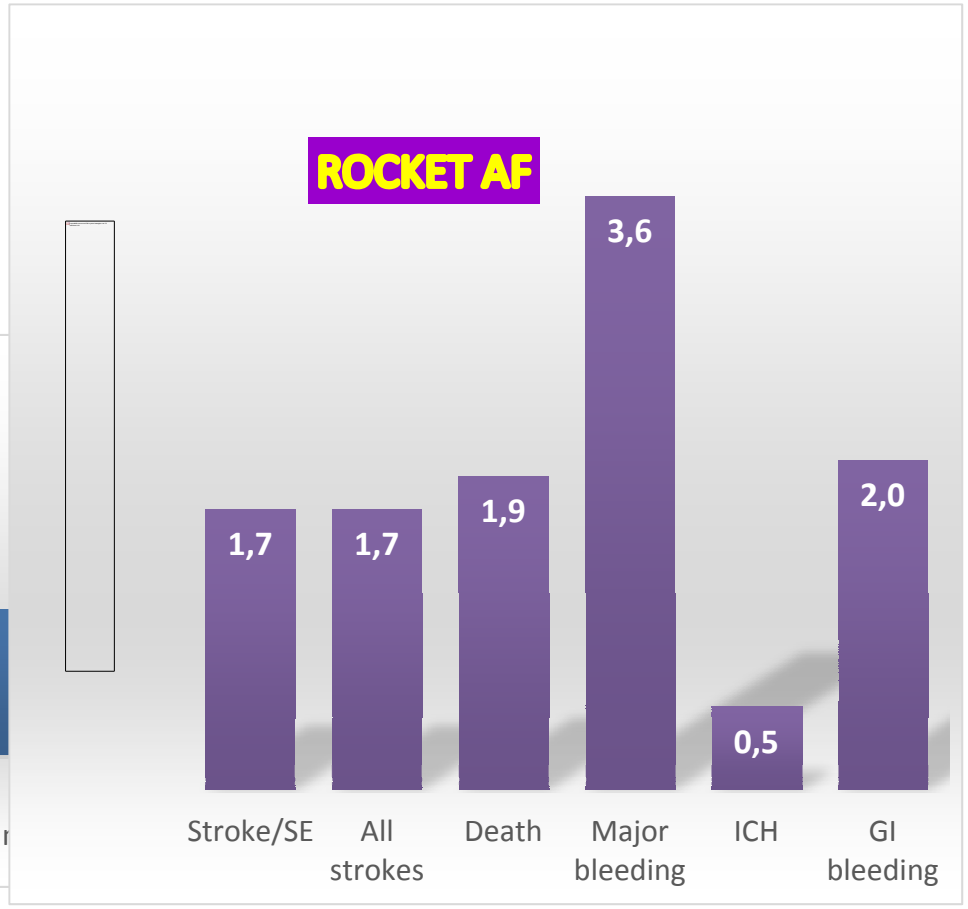
*Exact referral dates for follow-up visits not defined (every 3 months recommended)
#In rivaroxaban discontinuation ≤1 year, observation period ends 30 days after last dose

www.clinicaltrials.gov/ct2/show/NCT01606995

# Comparison of Main Outcomes: XANTUS versus ROCKET AF

| | $CHADS_2$ | Prior stroke# |
|---|---|---|
| ROCKET AF[1] | 3.5 | 55% |
| XANTUS[2] | 2.0 | 19% |




#Includes prior stroke, SE or TIA; *Events per 100 patient-years

1. Patel MR *et al, N Engl J Med* 2011;365:883–891; 2. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

# XANTUS Summary

- XANTUS is the first large, international prospective study to describe rivaroxaban use in a broad patient population with NVAF
  - Patients were at lower overall risk than in the phase III ROCKET AF trial
- Over 96% patients receiving rivaroxaban did not experience any of the outcomes of stroke/SE, treatment-emergent major bleeding or all-cause death
- **In XANTUS, rivaroxaban demonstrated low rates of stroke/SE and major bleeding, including intracranial and GI bleeding**
  - Incidences of these outcomes generally increased with higher stroke risk scores
  - Major bleeding was mostly treated conservatively; reversal agents were rarely used
- Treatment **persistence** and patient satisfaction were high
  - 80% of patients remained on rivaroxaban
  - 75% reported they were satisfied with their treatment at 1 year



1. Camm AJ *et al*, *Eur Heart J* 2015; doi: 10.1093/eurheartj/ehv466

# Rivaroxaban per la prevenzione dell'ictus in pazienti con fibrillazione atriale: risultati di una valutazione di HTA

## Health Technology Assessment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# Apixaban

Terzo NOAC, approvato da meno tempo rispetto a dabigatran e rivaroxaban. Non ci sono motivi per pensare che nel mondo reale debba comportarsi in modo diverso rispetto agli altri due NOAC……anzi

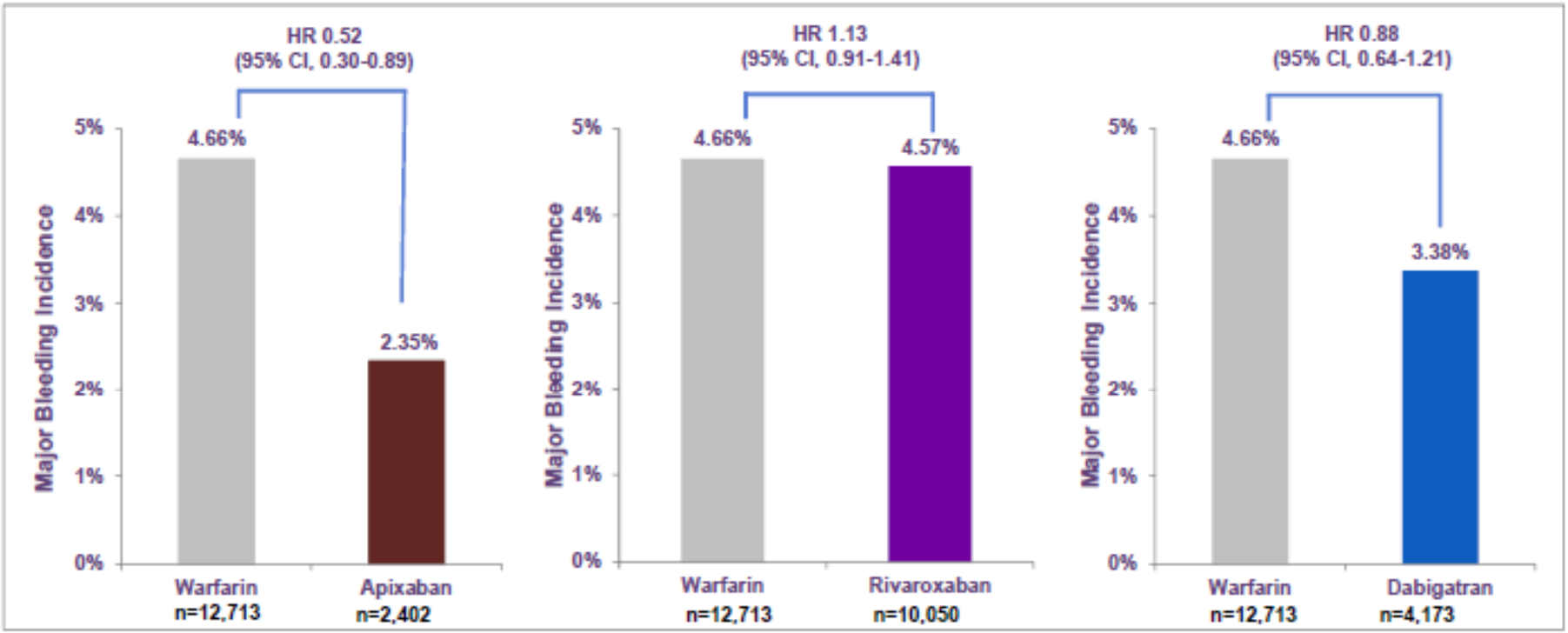
# Real World Comparison Of Major Bleeding Risk Among Non-valvular Atrial Fibrillation Patients Newly Initiated On Apixaban, Dabigatran, Rivaroxaban Or Warfarin

Gregory Y H Lip[1], Xianying Pan[2], Shital Kamble[2], Hugh Kawabata[2], Jack Mardekian[3], Cristina Masseria[3], Amanda Bruno[2], and Hemant Phatak[2*]

*[1]University of Birmingham, Birmingham, UK; [2]Bristol-Myers Squibb, Princeton, NJ; [3]Pfizer, Inc, New York, NY*

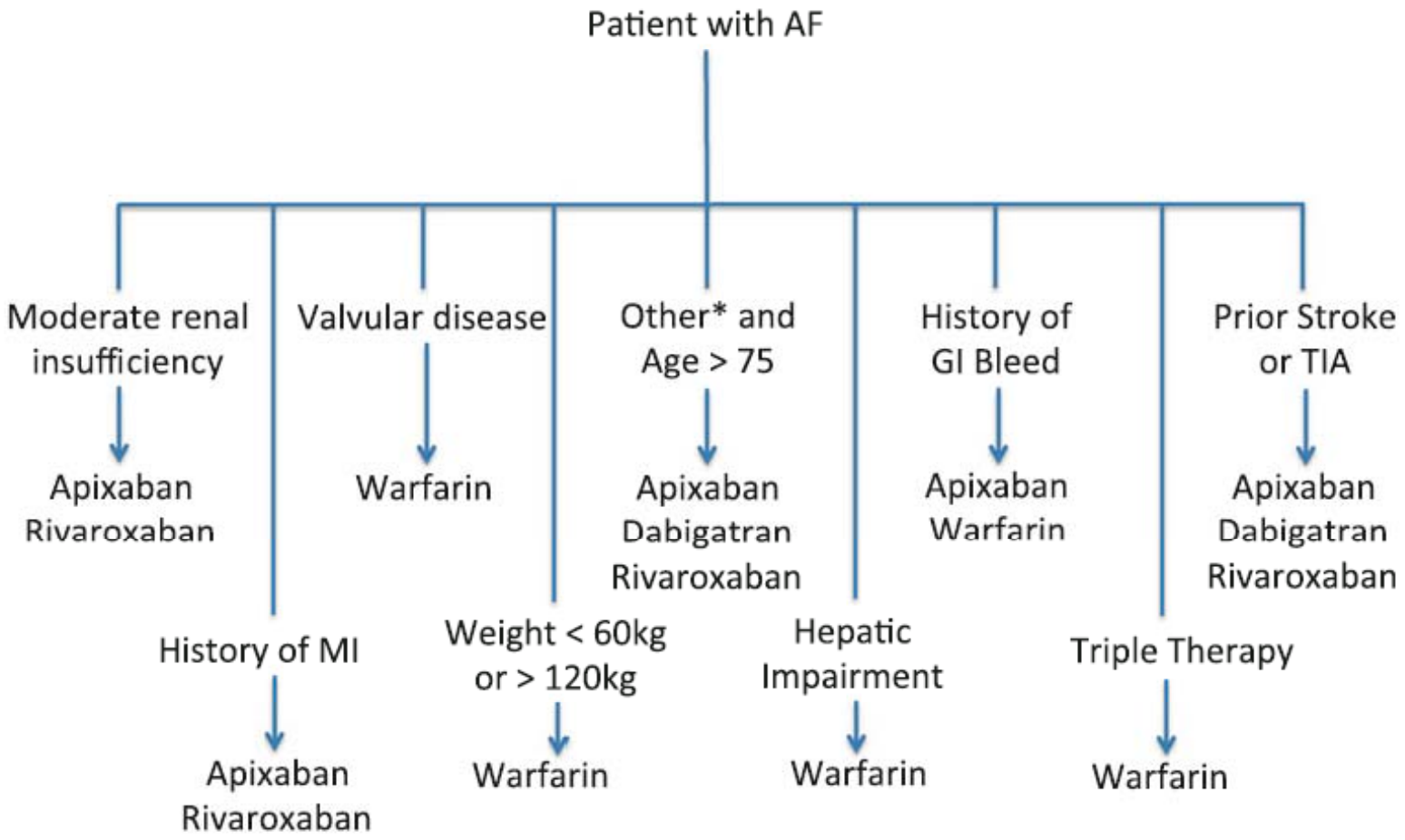
**At the time of research, Hemant Phatak was an employee of BMS*

Figure 3. Incidence Rates of Major Bleeding (Inpatient Bleeding per 100 person-year) and Adjusted Hazard Ratios for Anticoagulant Initiation – Apixaban, Rivaroxaban, and Dabigatran Compared to Warfarin*




* Hazard ratios (HR) are adjusted HRs based on Cox proportional hazards model adjusted for: age, sex, region, embolic or primary ischemic stroke, dyspepsia or stomach discomfort, congestive heart failure, coronary artery disease, diabetes, hypertension, renal disease, myocardial infarction, history of stroke or transient ischemic attack, history of bleeding, Charlson comorbidity index, and baseline medications including angiotensin converting enzyme inhibitor, amiodarone, angiotensin receptor blocker, beta blocker, H2- receptor antagonist, proton pump inhibitor, and statins.

# Quale NOAC ? e a chi ?




* Patients without renal insufficiency, history of MI, valvular disease, weight < 60kg, weight > 120kg, hepatic impairment, triple therapy, history of GI bleed, or prior stroke/TIA

SD. Pokorney et al. J Thromb Thrombolysis (2013) 36:163–174

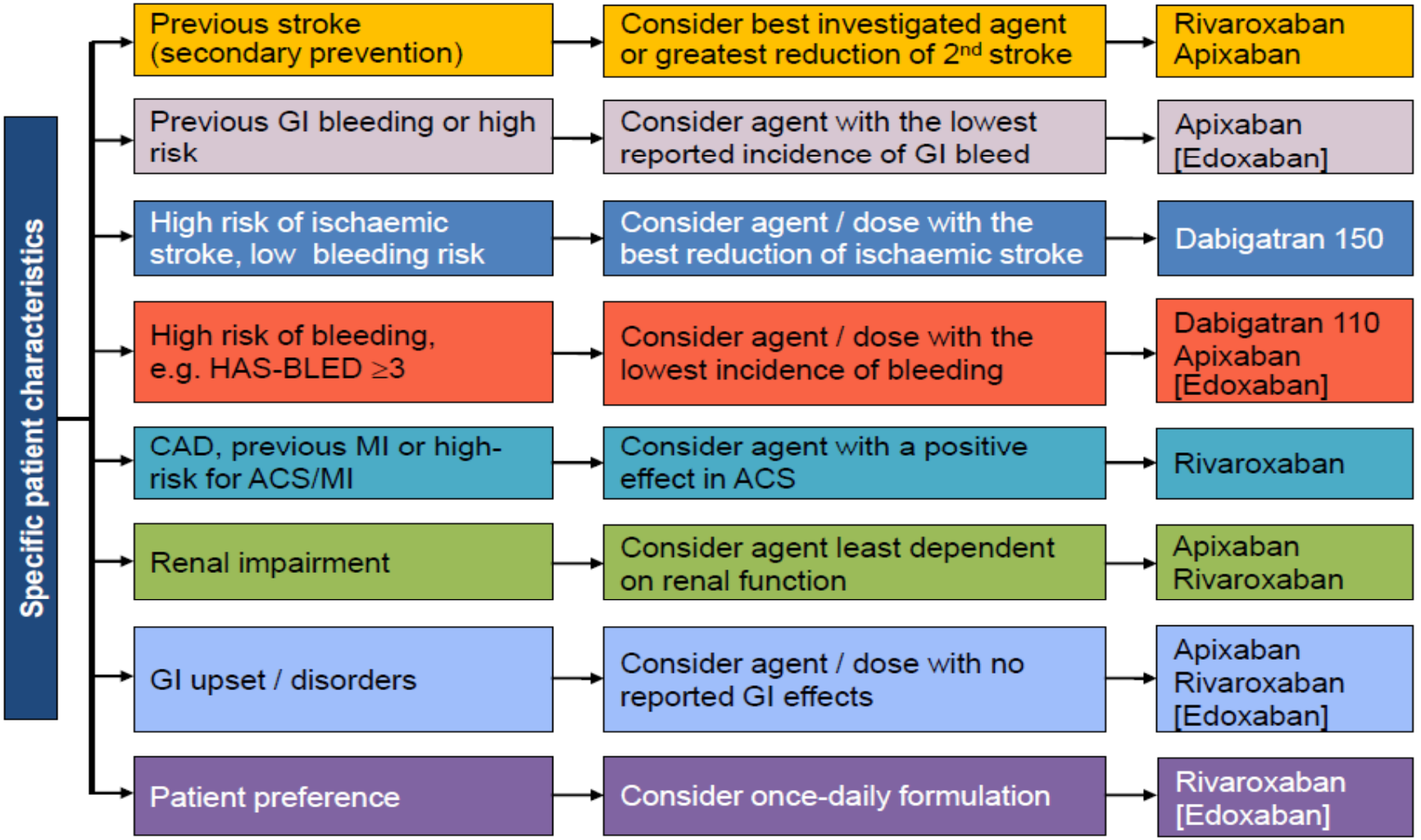
**Table 3: Major efficacy (analyzed as intention to treat) and safety outcomes in the atrial fibrillation studies (10–12).** Hazard ratios or relative risks are in relation to warfarin and are in bold type when showing a statistically significant reduction.

| Efficacy (reduction of stroke or systemic embolism) | Safety (major bleeding) |
|---|---|
| Best | |
| Dabigatran 150 mg BID<br>**RR 0.66 (95% CI, 0.53–0.82)** | Edoxaban 30 mg daily<br>**HR 0.47 (97.5% CI, 0.41–0.55)** |
| Apixaban 5 mg BID<br>**HR 0.79 (95% CI, 0.66–0.95)** | Apixaban 5 mg BID<br>**HR 0.69 (95% CI, 0.60–0.80)** |
| Edoxaban 60 mg daily<br>HR 0.87 (97.5% CI, 0.73–1.04) | Dabigatran 110 mg BID<br>**RR 0.80 (95% CI, 0.69–0.93)** |
| Rivaroxaban 20 mg daily<br>HR 0.88 (95% CI, 0.74–1.03) | Edoxaban 60 mg daily<br>**HR 0.80 (97.5% CI, 0.71–0.91)** |
| Dabigatran 110 mg BID<br>RR 0.91 (95% CI, 0.74–1.11) | Dabigatran 150 mg BID<br>RR 0.93 (95% CI, 0.81–1.07) |
| Edoxaban 30 mg daily<br>HR 1.13 (97.5% CI, 0.96–1.34) | Rivaroxaban 20 mg daily<br>HR 1.04 (95% CI, 0.90–1.20) |
| Worst* | |

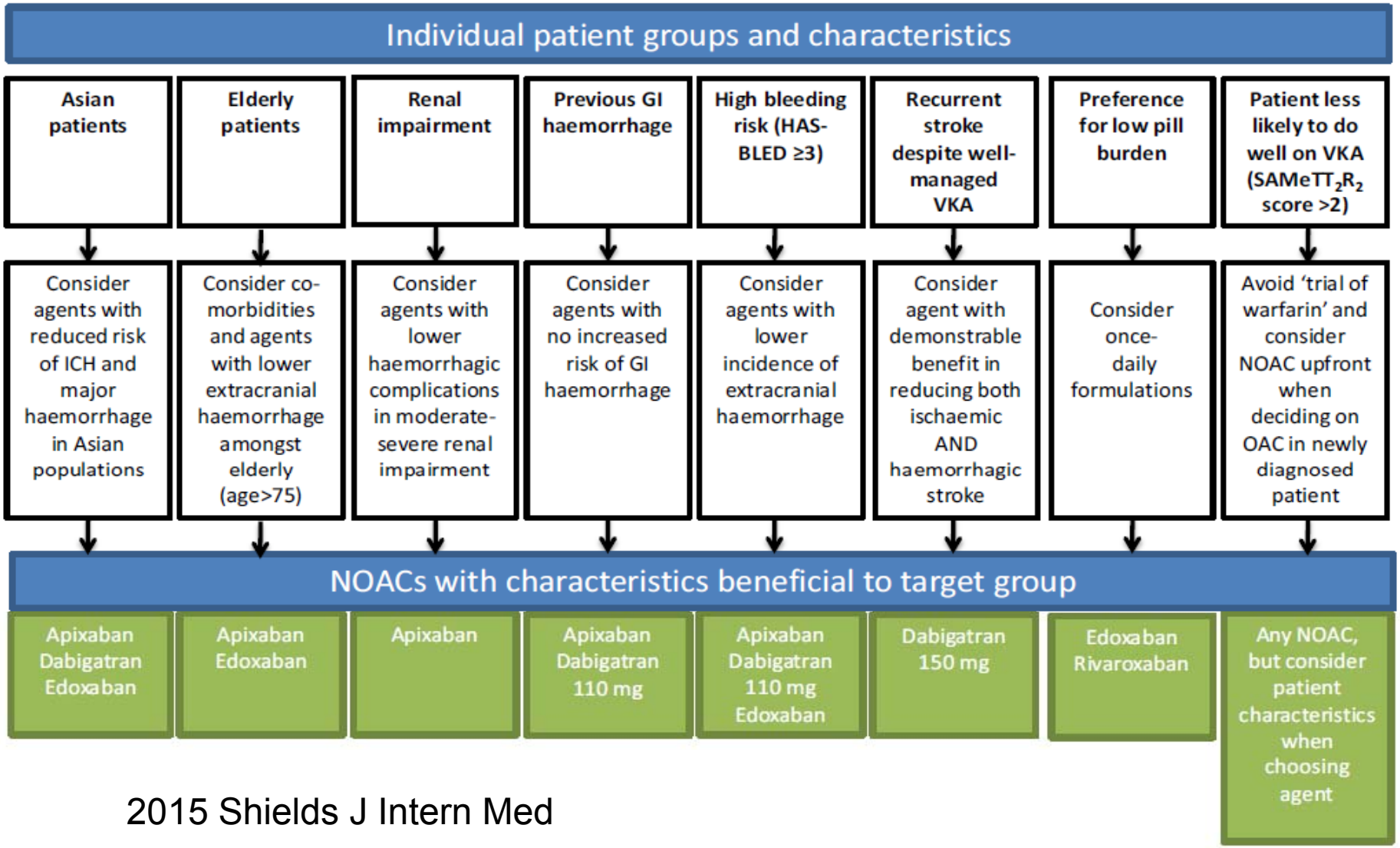
RR, relative risk; HR, hazard ratio; CI, confidence interval; BID, twice daily.
*Note that "worst" risk estimate is still non-inferior to warfarin.

**Schulman 2014 TH**

# Pointers towards which DOAC to choose




Adapted from Savelieva and Camm. Clin Cardiol 2014;37:32–47

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# Conclusioni

1. Contrariamente a quello che solitamente succede, dove i risultati dei trials sono in parte mitigati dalle analisi dei registri, nel caso dei NOAC i registri confermano e anche amplificano i benefici osservati negli studi registrativi

2. Non dobbiamo quindi aver paura di utilizzare questi farmaci, perché a lungo termine i benefici saranno evidenti

3. C'e' pero' necessità di un monitoraggio clinico :

- I NOACs sono anticoagulanti e come tali possono causare sanguinamenti.

- Tutti i NOACs hanno interazioni farmacologiche.
- I pazienti con FA sono una popolazione di pazienti «fragili».

- I pazienti dovrebbero, anzi devono, essere rivisti ad intervalli di tempo prestabiliti.

- Il monitoraggio della terapia può essere eseguito dallo specialista, dal MMG o dal centro di riferimento, purchè medico competente…

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